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Testing Novel Models of Gene–Environment Interaction Across the Transdiagnostic Mental Health Spectrum

Valeria Lavín Gutiérrez

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Universitat Autònoma de Barcelona

Facultat de Psicologia

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Doctorat en Psicología Clínica i de la Salut

DOCTORAL THESIS

Testing Novel Models of Gene–Environment Interaction Across the Transdiagnostic Mental Health Spectrum

by

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Apenas expresamos algo lo empobrecemos singularmente. Creemos que nos hemos sumergido en las profundidades de los abismos y cuando volvemos a la superficie la gota de agua que pende de la pálida punta de nuestros dedos ya no se parece al mar del que procede. Creemos que hemos descubierto en una gruta maravillosos tesoros y cuando volvemos a la luz del día sólo traemos con nosotros piedras falsas y trozos de vidrio; y sin embargo en las tinieblas relumbra aún, inmutable, el tesoro.

Maurice Maeterlinck

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ABBREVIATIONS

ADHD — Attention-Deficit/Hyperactivity Disorder

AIC — Akaike Information Criterion

ASD — Autism Spectrum Disorder

AUC — Area Under the Curve

BD — Bipolar Disorder

BLISS-II — Barcelona Longitudinal Investigation of Schizotypy Study 2

CI — Confidence Interval

CNVs — Copy Number Variants

DNA — Deoxyribonucleic Acid

DS — Differential Susceptibility

DSM — Diagnostic and Statistical Manual of Mental Disorders

ESM — Experience Sampling Methodology

ES-SCZ — Exposome Score for Schizophrenia

G×E — Gene-by-Environment Interaction

GWAS — Genome-Wide Association Study

GWEIS — Genome-Wide Environment Interaction Study

HiTOP — Hierarchical Taxonomy of Psychopathology

ICD — International Classification of Diseases

LEGIT — Latent Environmental and Genetic InTeraction

MAF — Minimum Allele Frequency

MDD — Major Depressive Disorder

MICE — Multivariate Imputation by Chained Equations

MZ — Monozygotic

OCD — Obsessive-Compulsive Disorder

PGC-CD — Cross-Disorder Group of the Psychiatric Genomics Consortium

PGS — Polygenic Score

PGS-ES — Polygenic Score for Environmental Sensitivity

PGS-BD — Polygenic Score for Bipolar Disorder

PGS-MDD — Polygenic Score for Major Depressive Disorder

PGS-SCZ — Polygenic Score for Schizophrenia

PGS-SCZ+BD — Polygenic Score for Shared Schizophrenia and Bipolar Disorder Liability

PLE — Psychotic-Like Experiences

PRS — Polygenic Risk Score

PTSD — Post-Traumatic Stress Disorder

RDoC — Research Domain Criteria

rGE — gene-environment correlation

RoS — Regions of Significance

RR — Relative Risk

SEM — Structural Equation Modelling

SNP — Single-Nucleotide Polymorphism

SNP×E — Single-Nucleotide Polymorphism-by-Environment Interaction

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INTRODUCTION

1. INTRODUCTION

Traditional frameworks in psychiatry have long conceptualized mental disorders as discrete categorical entities defined by distinct diagnostic boundaries and driven by specific genetic and environmental factors. However, converging evidence from epidemiology, psychiatric genetics, and clinical and developmental psychopathology has progressively challenged this view, pointing instead to a multifactorial, transdiagnostic, and dimensional understanding of mental health.

Early evidence from twin and family studies established that psychiatric disorders are substantially heritable (Polderman et al., 2015; Plomin, 2023), and the advent of genome-wide association studies (GWAS) raised expectations that this heritable liability could be mapped onto identifiable molecular variants. Yet SNP-based heritability estimates from GWAS explain only a fraction of the variance captured by quantitative genetic studies, a discrepancy known as the "missing heritability" gap (Manolio et al., 2009). Rather than the small number of large-effect variants initially anticipated, GWAS have revealed that psychiatric risk is highly polygenic, distributed across thousands of common variants each contributing a minute proportion of variance (Visscher et al., 2021; Smeland et al., 2025). These variants are also markedly pleiotropic, with the same genetic signals conferring risk across multiple disorders and extending to adaptive traits (Hindley et al., 2022), which suggests that the common-variant polygenic architecture of psychiatric disorders captures not only disorder-specific liability but a broader continuum of human phenotypic variability.

Environmental research has similarly moved from single exposures toward more comprehensive frameworks, driven by growing recognition that environmental factors mirror genetic complexity in its scope: exposures are also pleiotropic, operate across multiple dimensions, vary in their effects depending on the developmental period in which they occur, and form interdependent networks (Gülöksüz et al., 2018). The exposome, defined as the totality of environmental exposures encountered across the lifespan (Wild, 2005; Gülöksüz et al., 2018), aims at capturing this complexity by modeling correlated exposures and estimating their weighted contribution to mental health outcomes. However, exposome work has predominantly focused on biological, chemical, and physical exposures, paradoxically underrepresenting psychosocial factors such as childhood adversity, social isolation or socioeconomic factors, despite these being among the most robustly established environmental determinants of psychopathology (Varese et al., 2012; Kirkbride et al., 2024). Additionally, positive experiences are largely excluded from exposome models, despite increasing evidence that they independently buffer against psychopathology and promote well-being over and above the effects of adversity (Bethell et al., 2019; Chen et al., 2019).

Finally, the predominant approach examining gene-environment interplay in psychiatry has been grounded in the diathesis–stress model, which conceptualizes genetic liability as conferring vulnerability specifically under adverse environments (Gottesman & Shields, 1972; Monroe & Simons, 1991). Although informative, this framework may provide only a partial account of G×E, as it has primarily emphasized the detrimental effects of adverse environments, which are considered merely triggers of individuals' genetic liability. Consequently, it overlooks the potential role of positive environmental experiences in shaping developmental outcomes and offers limited insight into the mechanisms underlying resilience, recovery, and positive adaptation.

The Differential Susceptibility (DS) model (Belsky et al., 2007; Ellis et al., 2011; Belsky & Pluess, 2013) offers a compelling alternative, proposing that certain genetic variants function as plasticity factors that heighten sensitivity to both negative and positive environments, yielding "for better and for worse" outcomes. This reframing also provides a coherent evolutionary account of the counterintuitive persistence of common small-effect risk variants in the population under sustained negative selection (Keller & Miller, 2006; Uher, 2009). In this sense, plasticity variants, which are not intrinsically pathogenic but conditionally expressed, would preserve a range of reactive phenotypes thus sustaining adaptive variability in the population (Belsky & Pluess, 2009; Dongen & Boomsma, 2013; Szöke et al., 2020).

The overarching aim of this thesis was to examine gene-environment interactions within the Differential Susceptibility framework by employing polygenic scores (PGS) indexing both environmental sensitivity and liability to psychiatric disorders, a comprehensive exposome approach to early psychosocial experiences, and a transdiagnostic perspective encompassing multiple domains of subclinical psychopathology and positive mental health across two independent cohorts: the Barcelona Longitudinal Investigation of Schizotypy and Sensitivity (BLISS-II; n = 941; Barrantes-Vidal et al., 2013a; Barrantes-Vidal et al., 2025c), and the TwinssCan cohort (n = 638; Pries et al., 2017), comprising both adolescents and young adults. Six empirical studies are organized across three thematic sections. **Section 1** presents methodological advancements for G×E research, refining the operationalization of early environment experiences through an exposome approach and developing an analytical pipeline for robust G×E testing under missing data. **Section 2** provides the core empirical work, testing competitive G×E models across both cohorts using PGS for environmental sensitivity and disorder-based PGSs of psychotic and mood disorders. **Section 3** develops and qualitatively evaluates, across both clinical and non-clinical participants, a new set of items for assessing environmental sensitivity in daily life through Ecological Momentary Assessment (EMA).

Findings derived from this thesis may contribute to a growing body of research that challenges deterministic, risk-focused conceptualizations of genetic liability and advances the understanding of how genetic and environmental factors jointly shape transdiagnostic trajectories of both vulnerability and resilience. Collectively, these contributions support a transdiagnostic, multifactorial model of mental health in which genetic and environmental influences jointly determine not only vulnerability to psychopathology but also the capacity for positive outcomes, an integration with meaningful implications for prevention and personalized intervention

BACKGROUND

2. BACKGROUND

2.1. Dimensional and Transdiagnostic Conceptualizations of Psychopathology

Growing evidence in mental health research is increasingly questioning the assumption that psychiatric disorders are best understood as discrete, independent categories. Traditional diagnostic systems such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Classification of Diseases* (ICD), have been valuable for clinical communication and treatment organization, but they fail to capture the complex, transdiagnostic nature of psychiatric conditions.

Diagnostic categories are often highly heterogeneous (Allsopp et al., 2019), comorbidity is the rule rather than the exception (McGrath et al., 2020), categorical diagnoses show limited correspondence with underlying biological mechanisms (Hyman, 2007) and they show only modest predictive value for prognosis or treatment response (Kendell & Jablensky, 2003). Moreover, longitudinal research has consistently pointed to heterotypic continuity (i.e., the transition from one disorder to another one across the lifespan) (Lahey et al., 2014; Shevlin et al., 2017), a pattern observed across internalizing, externalizing, and neurodevelopmental domains, including the psychosis and affective disorders spectra. More broadly, the developmental unfolding of psychopathology, whereby early undifferentiated presentations give way to diverse adult outcomes (Shevlin et al., 2017; McGorry et al., 2018), further underscores that categorical models fail to capture the dynamic, multidimensional, and developmentally unfolding nature of psychopathology.

2.1.1. The Psychosis Continuum

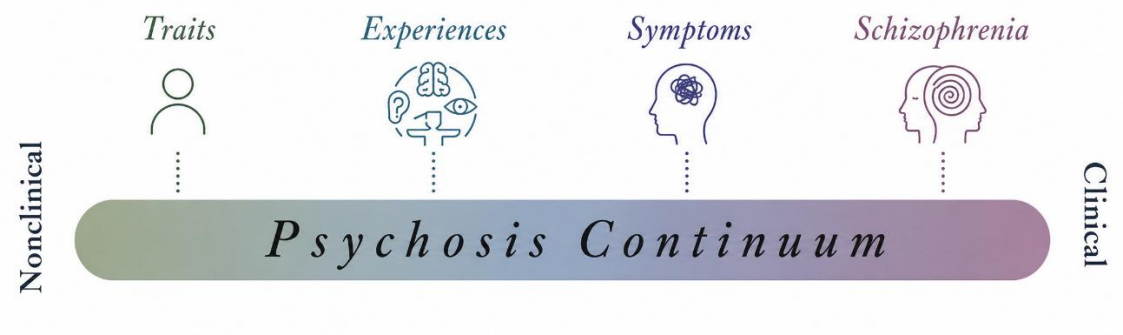
Evidence from the field of psychosis illustrates a particularly compelling case for dimensional continuity. Longitudinal studies have shown that schizotypy traits show relative temporal stability and show predictive validity of clinical and subclinical psychosis expressions. This initial evidence is consistent with epidemiological findings indicating that milder forms of psychotic symptoms, e.g., psychotic-like experiences (PLE), are present in approximately 5–7% of the general adult population, with higher rates in childhood and adolescence (Linscott & van Os, 2013; Staines et al., 2023). In most cases these experiences are attenuated and transient, though a meaningful proportion persist over time (~30%), with a minority eventually developing a clinical psychotic disorder (Van Os & Reininghaus, 2016; Staines et al., 2023). This is consistent with earlier dimensional conceptualizations of psychopathology in general, and psychosis in particular, suggesting that psychosis is expressed across a broad dynamic continuum of individual differences in personality, symptoms, and impairment—ranging from nonclinical manifestations (e.g., PLE) to full-blown clinical presentations (e.g., schizophrenia-spectrum disorders) (Claridge, 1997; Gülöksüz & van Os, 2018, 2021).

This phenotypic continuity is mirrored by etiological continuity: genetic (Mistry et al., 2018; Legge et al., 2019) and environmental (Van Os et al., 2010; Pignon et al., 2021) risk factors associated with schizophrenia are likewise implicated in psychotic experiences in the general population. This extended psychosis-proneness phenotype has been referred to as schizotypy (Barrantes-Vidal et al., 2015; Kwapil & Barrantes-Vidal, 2015; Grant et al., 2018;

see Figure 1), is hypothesized to emerge from the same causative factors operate across the full continuum, and psychotic features differ in degree of severity and dysfunction rather than in kind (Barrantes-Vidal et al., 2015). From this perspective, schizophrenia is not a categorically distinct entity but rather the extreme, poor-outcome end of a complex and much broader phenotypic spectrum (Gülöksüz & van Os, 2018).

Importantly, the heterogeneity of schizotypy has shown to be represented by a three-dimensional structure of positive, negative and disorganized schizotypy (Kwapil & Barrantes-Vidal, 2015; Kwapil et al., 2018; Kemp et al., 2021), replicating the most supported model of positive, negative and disorganized symptomatology in schizophrenia (Lenzenweger & Dworkin, 1996; Liddle, 1987). Critically, these dimensions have demonstrated prospective predictive validity for psychopathology and functional impairment across longitudinal programmes, including the pioneering reanalysis of the Chapmans' ten-year study (Kwapil et al., 2013) and the Barcelona Longitudinal Investigation of Schizotypy (Barrantes-Vidal & Kwapil, 2025). This makes schizotypy a very useful construct for understanding mechanisms involved in the transition from predisposition to disorder, as well as risk factors and mechanisms underlying schizophrenia without clinical, psychosocial, pharmacological and stigma-related confounds (Kwapil & Barrantes-Vidal, 2015; Grant et al., 2018).

Figure 1. Schizotypy or the extended psychosis phenotype



2.1.2. The Extended Psychosis Continuum as a Transdiagnostic Construct

Consistent with early psychopathology theorization and clinical observation, the extended psychosis phenotype is increasingly recognized as a transdiagnostic phenomenon, spreading well beyond the boundaries of psychotic disorders. Psychotic experiences are documented across a broad range of psychiatric conditions: they are twice as prevalent in depression and anxiety as in the general population (Wigman et al., 2012; Jeppesen et al., 2015; Kelleher & Cannon, 2021), and show substantial co-occurrence with Obsessive-Compulsive Disorder (OCD; Aonso-Diego et al., 2025), disorder eating behaviors (Solmi et al., 2018), as well as with Attention Deficit Hyperactivity Disorder (ADHD; Gelner et al., 2024) and Autistic Spectrum Disorder (ASD; Rowe et al., 2025). Crucially, a recent meta-analysis by Uher et al. (2024) identified several psychopathological antecedents associated with the subsequent onset of major depressive disorder (MDD), bipolar disorder (BD), and psychotic disorders, many of which showed transdiagnostic relevance. For instance, depressive symptoms significantly increased the risk of later developing any of these three disorders (Relative Risk (RR) = 1.76, 95% CI 1.53–2.01), while psychotic symptoms conferred an even stronger transdiagnostic risk

(RR = 2.31, 95% CI 1.85–2.88). Basic symptoms (i.e., recently emerging abnormalities of perception and cognition) and schizotypy were also significantly associated with the onset of both psychotic and depressive disorders, and psychotic symptoms predicted later MDD more strongly than subthreshold depressive symptoms, whereas depressive symptoms predicted later psychotic disorders more strongly than psychotic antecedents themselves (Uher et al., 2024).

2.1.3. Towards a Broader Conceptualization of Mental Health

These findings have motivated broader, transdiagnostic empirical models of psychopathology, such as the p-factor, a general dimension spanning internalizing, externalizing, and thought disorder domains (Caspi et al., 2014; Caspi & Moffitt, 2018), which has shown that a substantial portion of variance in psychopathology reflects shared transdiagnostic liability rather than disorder-specific processes. The shift towards more dimensional approaches is further reflected in the emergence of alternative nosological frameworks such as the Research Domain Criteria (RDoC; Insel et al., 2010), which organizes psychopathology around neuroscientific constructs and functional dimensions cutting across diagnostic boundaries, and the Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov et al., 2017), which arranges psychopathological syndromes in a data-driven hierarchical structure ranging from broad spectra to narrow symptom clusters.

Nevertheless, these advances share an important limitation: they remain focused on the symptom end of the mental health spectrum and do not integrate well-being, functioning, and other indicators of positive mental health. This is consequential, because the absence of psychopathology does not guarantee the presence of positive mental health, and vice versa. The dual continua model (Keyes, 2002; Suldo & Schaffer, 2008; Westerhof & Keyes, 2009) formalizes this insight by conceptualizing psychopathology and well-being as related but distinct dimensions that can coexist independently: individuals with psychological disorders may experience high well-being, and those free of diagnosable conditions may nonetheless show poor flourishing (Iasiello & Van Agteren, 2020; Grych et al., 2020). A comprehensive account of mental health, and of the factors that shape it, therefore requires moving beyond symptom-centric frameworks, to include the assessment of the full spectrum of mental health outcomes.

2.2. Study of the Causes of Mental Health Disorders

Psychiatric disorders have long been considered highly heritable, yet heritability estimates account for only a modest proportion of phenotypic variance, and growing epidemiological evidence has established environmental factors as substantial contributors to psychiatric risk. Current evidence points to a multifactorial aetiology in which polygenic and poly-environmental influences jointly shape disorder liability. As outlined in Section 1, the phenotypic boundaries between psychiatric disorders are considerably less clear-cut than traditional categorical models assume. The inability of such models to capture the multidimensional and continuous nature of psychopathology, together with the widespread genetic pleiotropy documented across disorders (see Section 2.1) and the broadly shared environmental risk factors (see Section 2.2), are collectively driving a shift toward a more transdiagnostic and multifactorial understanding of psychiatric aetiology.

2.2.1. Genetic Factors: From candidate genes to polygenic architectures

Twin, family, and adoption studies (i.e., behavioral quantitative genetics) established, across the twentieth century, that genetic factors influence virtually all human behavioral traits and psychiatric conditions (Plomin, 2023), with heritability averaging approximately 50% across the behavioral phenome (Polderman et al., 2015). Within psychopathology, heritability was determined to be substantial (Nemoda et al., 2011), with estimates varying across disorders, ranging from high (e.g., schizophrenia and bipolar disorder: 60 –85%) to moderate (e.g., MDD: ~40%) (Flint et al., 2014; Hilker et al., 2018; Kendler et al., 2018; see Figure 2).

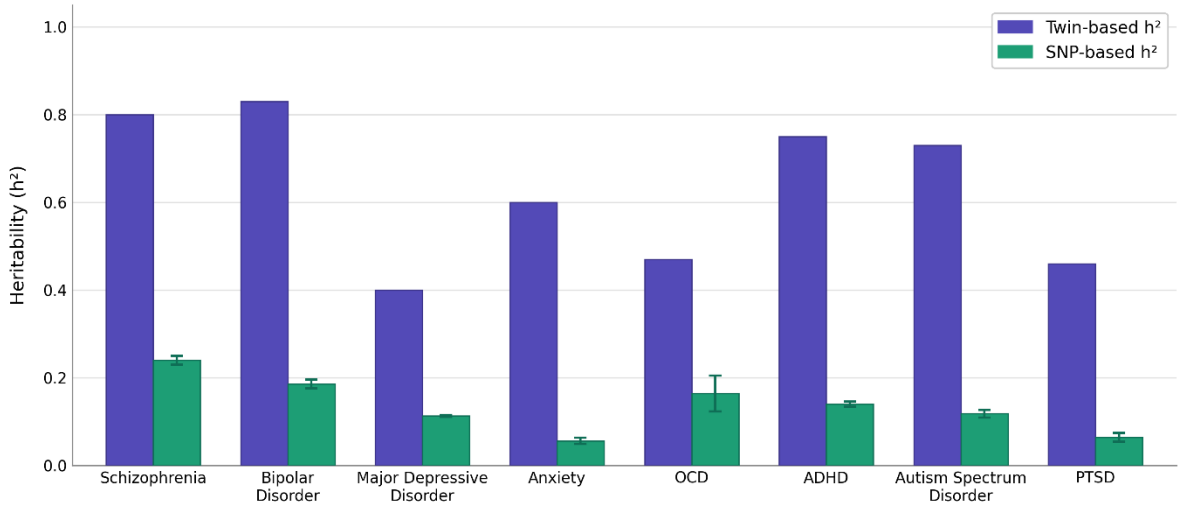
Early molecular genetic studies relying on candidate-gene designs were grounded in the expectation that a limited number of allelic variants of large effect would account for a substantial proportion of this heritable liability, but they yielded inconsistent results in replication efforts (Border et al., 2019; Plomin, 2023). A major methodological breakthrough, the advent of DNA microarray technology, enabled the simultaneous assay of hundreds of thousands of single-nucleotide polymorphisms (SNPs) across the genome and made possible the emergence of genome-wide association studies (GWAS)—agnostic, hypothesis-free scans conducted in large samples of unrelated individuals. As GWAS sample sizes and statistical power increased, a consistent pattern emerged: rather than a small number of variants of large effect, psychiatric disorders were shown to be highly polygenic, with risk distributed across thousands of common variants, each contributing only a minute proportion of variance (Visscher et al., 2021; Smeland et al., 2025). GWAS index mostly the common-variant layer of genetic architecture (SNPs with minimum allele frequency (MAF) > 1%), while rarer but often more penetrant structural variants, such as copy number variants (CNVs), contribute a distinct, complementary signal to disorder risk. Nevertheless, for most adult-onset psychiatric disorders, the bulk of population-level genetic risk is attributable to common variants of small effect rather than rare large-effect mutations, the latter tending to produce more severe and earlier-onset presentations (O'Connor et al., 2019).

A key applied output of GWAS is the polygenic score (PGS, also termed polygenic risk score or PRS): a single individual-level index computed by summing alleles associated with a phenotype, weighted by their GWAS-derived effect sizes (Lewis & Vassos, 2020). PGS thus aggregate the cumulative burden of common risk alleles into a continuous probabilistic estimate of genetic liability (Furrer & Turkheimer, 2026) and have since become the established tool for quantifying individual-level genetic liability in psychiatric research, demonstrating predictive validity across both clinical (Lewis & Vassos, 2020) and non-clinical populations (e.g., Musliner et al., 2019).

Another important insight emerging from accumulating GWAS evidence is the remarkable extent of genetic pleiotropy across psychiatric disorders. After early studies mapped the genetic architecture of individual disorders, large-scale cross-disorder analyses, such as those led by the Cross-Disorder Group of the Psychiatric Genomics Consortium (PGC-CD), demonstrated that many of the same genetic variants contribute to increase the risk of multiple diagnoses. For instance, a meta-analysis spanning eight psychiatric disorders identified 109 loci influencing at least two conditions (PGC-CD, 2019). Subsequent work has reinforced and extended evidence for a shared genetic architecture across disorders: substantial genetic correlations are

consistently observed across disorders (Owen et al., 2025; Smeland et al., 2025; Tylee et al., 2022) and polygenic scores derived from disorder-specific GWAS typically associate with broad dimensions of psychopathology rather than mapping cleanly onto single diagnoses (Neumann, et al., 2022). This pattern has recently been operationalized in a *p-factor-derived* polygenic score, which has been shown to be associated with transdiagnostic symptom liability more effectively than disorder-specific PGS (Keser et al., 2026). Extending this work at the genomic level, the most comprehensive analysis to date, integrating SNP-level data across 14 psychiatric disorders using genomic structural equation modelling (SEM), found that the bulk of shared genetic signal is captured by a higher-order genomic *p-factor* alongside a small number of broader transdiagnostic factors, with relatively little variance attributable to disorder-specific genetic signals (Grotzinger et al., 2026).

Figure 2. Family-based versus SNP-based heritability across eight psychiatric disorders



Note. Adapted from Andreassen et al. (2023). Twin-based heritability estimates are drawn from landmark twin studies as compiled in Andreassen et al. (2023). SNP-based heritability estimates are derived from the most recent GWAS for each disorder: schizophrenia (Trubetskoy et al., 2022), bipolar disorder (Mullins et al., 2021), major depressive disorder (Levey et al., 2021), anxiety (Levey et al., 2020), OCD (Ström et al., 2021), ADHD (Demontis et al., 2023), ASD (Grove et al., 2019), and PTSD (Stein et al., 2021). Error bars represent standard errors (SE) for SNP-based estimates only.

Despite the continuous advances driven by GWAS, a fundamental tension emerged as estimates of SNP-based heritability (calculated from the common variants identified in GWAS) explain only a fraction of the heritability established by twin and family studies, a discrepancy called the *missing heritability* problem (Manolio et al., 2009; see Figure 2). This gap likely reflects multiple contributing factors, including, for example, insufficient statistical power to detect loci of very small effect, incomplete capture of rare variants by standard genotyping arrays, and the possibility that twin-based estimates are themselves inflated by non-additive genetic effects such as gene–gene and gene–environment interactions (Zuk et al., 2012; Owen et al., 2021; Brandes et al., 2022). Crucially, it also suggests that genetic factors may account for a smaller proportion of psychiatric risk than originally anticipated.

All these findings collectively suggest that genetic risk for psychiatric disorders may be more modest, more diffuse, and less diagnosis-specific than originally anticipated, pointing out the limits of a purely genetic and categorically organized account of psychiatric risk, and

driving increasing attention to the role of environmental factors and their interplay with genetic predisposition.

2.2.2. Environmental Factors: From single exposures to the Exposome

Earlier research on the role of the environment in the aetiology of mental disorders focused on the potential of biological insults (e.g., obstetric complications, prenatal infections) to disrupt early brain maturation and confer neurological vulnerability to later symptomatology. In this framework, the environment functioned primarily as a neurodevelopmental disruptor acting upon an underlying genetic predisposition (e.g., Nuechterlein, 1986; Walker & Diforio, 1997).

Limitations in the explanatory power of genetic factors alone (i.e., heritability gap) together with increasingly robust psychosocial epidemiological research, particularly in the field of psychosis (van Os et al., 2010; Stilo & Murray, 2019), contributed to the growing recognition that environmental risk operated at multiple levels. This broader conceptualization encompasses macro-level social factors such as urbanicity (Van Os et al., 2001; Pignon et al., 2023), socioeconomic (Lund et al., 2010), and migration status (Cantor-Graae & Selten, 2005), as well as micro-level exposures including childhood adversity (Read et al., 2005; Read & Bentall, 2010; Alameda et al., 2021) and cannabis use (Di Forti et al., 2019).

Psychosocial stressors operate across different developmental periods (Zwicker et al., 2018), with childhood and adolescence constituting a critical window in which exposure to psychosocial stress carries particular weight for later psychopathological manifestations (Dean & Murray, 2005; Zwicker et al., 2018). Childhood adversity is among the most extensively studied factor, and has been consistently associated with increased risk for both clinical and subclinical psychosis (Sheinbaum & Barrantes-Vidal, 2015; Radua et al., 2018; Williams et al., 2018; Stilo & Murray, 2019; Cullen et al., 2023). A recent meta-analysis synthesizing 183 studies (N = 249,265) found significant associations between early adversity and psychosis across all study types, with an overall odds ratio of 2.80 (95% CI = 2.18–3.60) (Zhou et al., 2025a). Further reinforcing a causal interpretation, research has demonstrated a dose-response relationship between childhood adversity and psychotic phenomena (Flinn et al., 2025), and that adversity exposure temporally precedes psychosis onset (McGrath et al., 2017).

Although widely studied in the context of schizophrenia, childhood adversity and other psychosocial risk factors extend to other psychiatric disorders, such as MDD, BD, anxiety, ADHD and Post-Traumatic Stress Disorder (PTSD; Kessler et al., 1997; McLaughlin et al., 2010; Overstreet et al., 2017; Lynch et al., 2021). Most environmental risk factors appear to be pleiotropic, with the same exposures conferring risk for a diverse range of psychopathological outcomes (Gülöksüz et al., 2015; Conway et al., 2018; Radhakrishnan et al., 2019; van Os et al., 2020; McLaughlin et al., 2020; Hogg et al., 2023) and being involved in psychological and cognitive multimorbidities (Zhou et al., 2025b).

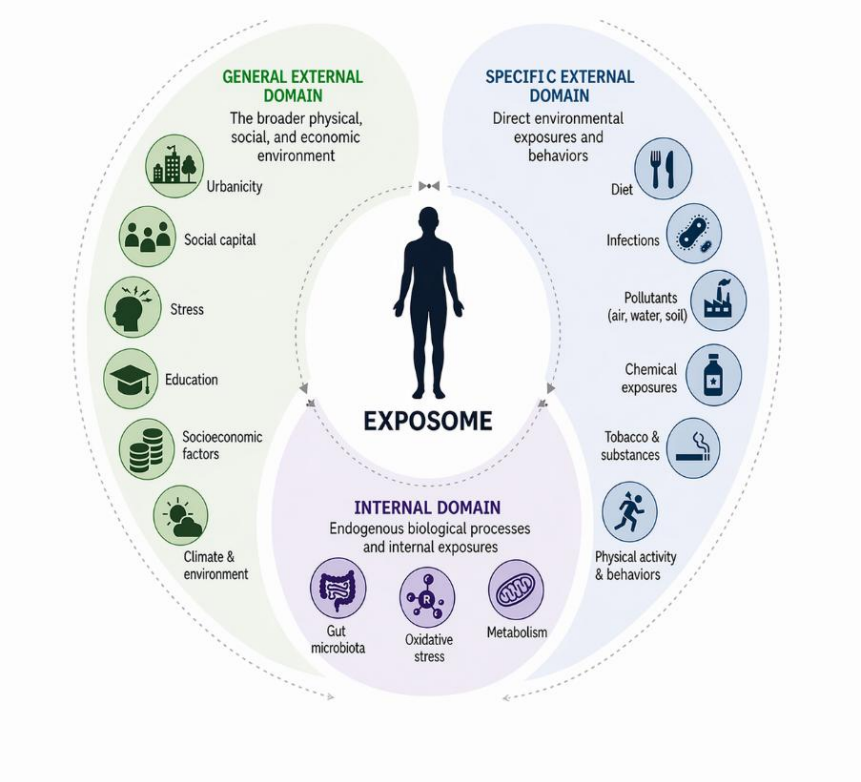
An expanding body of research extending environmental risk beyond the psychosocial domain to biological factors (e.g., gut–brain axis, microbiome, oxidative stress), physical exposures (e.g., air pollution), and chemical agents (e.g., heavy metals, endocrine disruptors), has established their contribution to the aetiology of mental disorders (Hollander et al., 2020).

This growing breadth of evidence points to a further, deeper challenge: the complexity of environmental risk rivals, if not surpasses, that of genetic factors. Exposures are pleiotropic and convergent—multiple exposures increase risk for the same disorder while a single exposure may confer risk across many (van Os et al., 2020); effects span the full continuum from subclinical to clinical presentations (Gülöksüz et al., 2018); timing matters, with the same exposure carrying different weight depending on the developmental period in which it occurs (Zwicker et al., 2018); and exposures do not act in isolation but form complex interdependent networks in which confounding, mediation, and moderation are the rule rather than the exception (Pries et al., 2021). Establishing causality under these conditions is methodologically challenging and demands frameworks capable of accommodating this heterogeneity.

2.2.2.1. The Exposome framework

To better capture the interdependency of environmental exposures and their cumulative effects, the exposome framework provides one holistic approach to studying the environmental contribution to disorder aetiology. Originally introduced in cancer epidemiology (Wild, 2005) and subsequently applied to psychiatry (Gülöksüz et al., 2018), it is defined as the totality of environmental exposures an individual encounters across the lifespan, encompassing three broad domains: a general external domain, a specific external domain, and an internal domain comprising endogenous biological factors (see Figure 3).

Figure 3. The Exposome: A multidomain framework of environmental exposures



The exposome can be operationalized using exposome scores, which account for correlations among exposures and estimate their weighted contribution to a given health outcome (Erzin & Gülöksüz, 2021). For instance, the exposome score for schizophrenia (ES-SCZ) has shown good discriminative ability for identifying clinical cases (AUC = 0.84) and

predicted poorer well-being and functioning over time (Pries et al., 2020, 2021), with its predictive utility extending transdiagnostically to subclinical psychopathology in non-clinical populations (Moore et al., 2022; Pries et al., 2022; Barzilay et al., 2022).

Beyond the ES-SCZ, most exposome research in mental health has predominantly focused on biological, physical, and chemical exposures, while social and psychosocial factors—paradoxically among the most robustly established in epidemiological research (Barzilay et al., 2022)—have remained underrepresented or included as confounders rather than as autonomous determinants of psychopathology (Gudi-Mindermann et al., 2023; Neufcourt et al., 2022; Vineis & Barouki, 2022). This is consequential because psychosocial factors—e.g., adversity, discrimination, social isolation, socioeconomic insecurity, or chronic stress—shape core psychological functions such as emotion regulation, cognition, stress responsivity, and interpersonal functioning, and are therefore more proximally constitutive of the processes through which psychopathology emerges, persists, or is buffered against (Kirkbride et al., 2024). To address this underrepresentation, Colomina et al.'s (2018) propose the "psychoexposome" which is a complementary psychological extension of exposome research more focused on capturing life experiences, psychosocial challenges, and adaptive and maladaptive behavior, along with their biological embedding through epigenetic, neuroendocrine, immune, and inflammatory pathways.

Furthermore, the majority of exposome studies in psychiatry have concentrated on single disorders and adverse exposures (Barzilay et al., 2022; Moore et al., 2022), leaving largely unexamined both the transdiagnostic scope of environmental risk and the potential protective role of positive exposures. This exclusive focus on adversity is particularly limiting given accumulating evidence that positive experiences confer protection against psychopathology and promote well-being independently of the effects of adversity (Sege & Browne, 2017; Butler et al., 2019; Chen et al., 2019; Bethell et al., 2019).

2.2.3. Gene-Environment Interaction

Increasing evidence that neither genetic nor environmental factors alone are sufficient to explain the heterogeneity of mental health outcomes; rather, it is their dynamic interplay that shapes individual trajectories of risk and resilience (Kendler et al., 1986; Plomin et al., 1994; Uher & Zwicker, 2017, Choi et al., 2022), brought gene-by-environment interactions (G×E) to the forefront of psychiatric research.

2.2.3.1. Biological Underpinnings of Gene-Environment Interaction

Genetic liability for psychiatric disorders is thought to manifest through its effects on the development of neural systems involved in symptomatology, including those underpinning affective processing, fear learning, and social cognition (Mehta et al., 2010; Teicher et al., 2016; Vedechkina et al., 2025). Critically, these same neural systems are also profoundly shaped by environmental exposures that become molecularly embedded in stress-regulatory systems (Tottenham et al., 2011; Miller et al., 2022) and sculpt stress-susceptible neural circuits in ways that overlap substantially with the substrates of genetic risk (Colich et al., 2020; McLaughlin et al., 2015; Teicher et al., 2019). Epigenetic research has illuminated one key molecular pathway underlying this convergence: life experiences, including early adversity, induce changes in

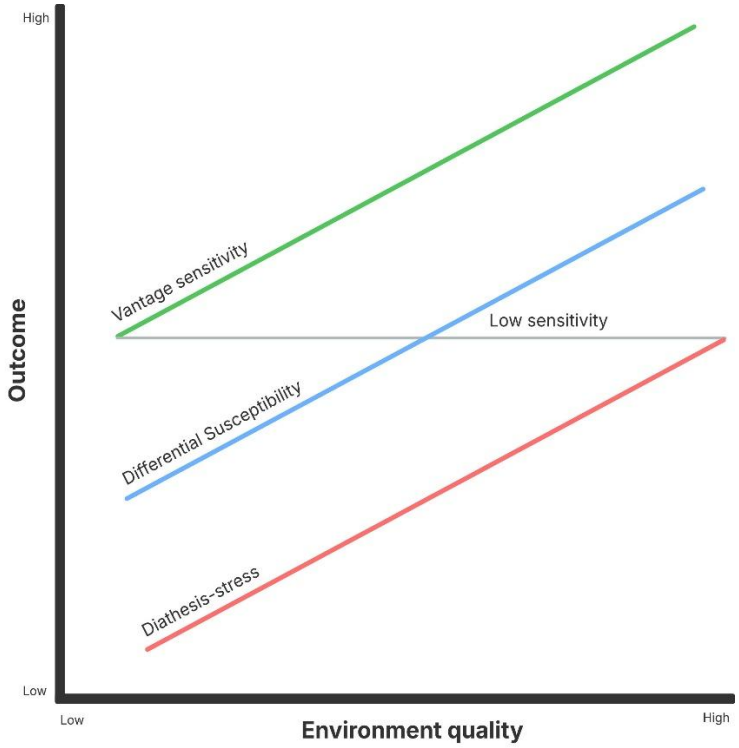
DNA methylation and chromatin structure that alter gene expression and, in turn, shape behavioural phenotypes (Cohen et al., 2007; McEwen, 2009; Rutten & Mill, 2009). Environmental exposures, then, do not simply trigger pre-existing genetic vulnerabilities but actively remodel the very neural systems through which genetic liability is expressed (Barker et al, 2018; Hoffmann, Sportelli, Ziller, & Spengler, 2017)

2.2.3.2. Theoretical Frameworks of Gene-Environment Interaction

Traditionally, G×E research has been grounded in the diathesis-stress model, in which genetic factors are conceptualized as risk-promoting influences that, in interaction with adverse environmental contexts, lead to psychopathology (Gottesman & Shields, 1972; Monroe & Simons, 1991). However, the growing complexity and dimensional nature of psychiatric risk—spanning extreme polygenicity, pervasive pleiotropy, and transdiagnostic environmental effects—is difficult to accommodate within a framework built around single genes, single stressors, and categorical disorder boundaries.

Alternatively, the Differential Susceptibility theory (DS; Belsky et al., 2007; Belsky & Pluess, 2009; Ellis et al., 2011) proposes that rather than solely encoding vulnerability, certain genetic variants may index a broader sensitivity or plasticity to the environmental context—that is, that the same genetic variants involved in amplifying the negative effects of adversity may also enhance the likelihood of benefiting from supportive contexts ("for better and for worse"; Belsky et al., 2007). While the DS model retains the diathesis-stress framework's recognition of adverse environmental effects, it differs fundamentally in reframing traditional "risk" genes as "susceptibility" genes that amplify susceptibility to the *full* spectrum of environmental conditions (Bakermans-Kranenburg, 2015; Fox & Beevers, 2016). A related model emerging from DS research is vantage sensitivity (Belsky & Pluess, 2013; Pluess et al., 2017), which is the mirror image of diathesis-stress and posits that certain genetic variants confer disproportionate benefit from positive environments without increasing vulnerability to negative ones—though it has been criticized for its limited theoretical and evolutionary grounding (Bakermans-Kranenburg & van IJzendoorn, 2015). A graphical representation of all three models is shown in Figure 4. This reframing is especially relevant given the polygenic, common-variant architecture of psychiatric disorders. Highly penetrant variants may persist through mutation-selection balance (i.e., where the rate of new mutations offsets their removal by natural selection) despite fitness costs, but common small-effect variants, the bulk of psychiatric genetic risk, are unlikely to remain frequent under sustained negative selection without some compensatory advantage (Keller & Miller, 2006; Uher, 2009). Plasticity variants offer a coherent evolutionary explanation: they are not intrinsically pathogenic but conditionally expressed, preserving a range of reactive phenotypes thus preserving adaptive variability in the population (Belsky & Pluess, 2009; Dongen & Boomsma, 2013; Szoke et al., 2020).

Figure 4. G×E Interaction Models



In order to target genetic variants associated with environmental susceptibility, Keers et al. (2016) conducted a GWAS of within-pair differences in emotional problems among monozygotic (MZ) twins. Because MZ twins share virtually 100% of their genetic material and, to a substantial degree, their rearing environment, systematic within-pair differences in emotional problems are unlikely to reflect genetic or shared environmental influences, and instead index susceptibility to non-shared environmental experiences. Polygenic scores for environmental susceptibility (PGS-ES) derived from this GWAS have shown to moderate the effects of a cognitive-behavioral intervention (Keers et al., 2016) and a family-based intervention (Lemery-Chalfant et al., 2018) on children's internalizing symptoms, following a DS pattern.

2.2.3.3. Statistical Approaches to Testing Gene-Environment Interaction

From a statistical point of view, testing for DS means testing for a *disordinal* interaction—one where the effect of the genetic factor on the outcome reverses direction depending on the level of the environmental predictor. In practical terms, the regression lines for high- and low-sensitivity individuals must cross within the observed range of the environment. This crossing point, the crossover, is the key parameter that distinguishes DS from ordinal interactions such as diathesis-stress or vantage sensitivity, where one group is consistently more affected than the other, but the direction of the effect never flips.

Conventional G×E regression methods can detect the presence of an interaction but were not designed to test the relative fit of competing forms, leaving the specific nature of the G×E interaction undetermined (Roisman et al., 2012). The competitive-confirmatory approach (Widaman et al., 2012; Belsky, Pluess & Widaman, 2013) was developed to addresses this shortcoming, by reparametrizing the regression model to directly estimate the crossover point

and using fit indices (AIC/BIC) to formally compare competing G×E models. The R package LEGIT (Latent Environmental and Genetic InTeraction; Jolicoeur-Martineau et al., 2020) was developed to perform this analysis. A two-stage workflow was later advocated by Belsky & Widaman (2018) in which standard regression is first used to establish the presence of a G×E interaction, before the competitive-confirmatory framework is applied to determine its form. Simulation studies show that the competitive-confirmatory approach substantially outperforms previous approaches, such as regions of significance (RoS) analysis (Roisman et al., 2012), in accuracy across a wide range of sample sizes and effect sizes (Jolicoeur-Martineau et al., 2020).

2.2.3.4. Ecological Assessment of Gene-Environment Interaction

While G×E research has focused predominantly on the impact of distal environmental factors such as major life events or childhood adversity, proximal psychosocial factors (e.g., minor daily hassles or momentary stress), have also shown robust predictive ability for psychopathology and subclinical symptom expression (Barrantes-Vidal et al., 2013; Reininghaus et al., 2016; Kwapil et al., 2020). Crucially, how these proximal exposures translate into outcomes is not uniform across individuals: person-level factors (P), such as momentary affect, cognitive appraisals, and stress reactivity, among others, shape how environmental inputs are perceived and processed, potentially mediating or moderating the expression of genetic predispositions in context. Experience Sampling Methodology (ESM), or Ecological Momentary Assessment (EMA), uses repeated real-time assessment of psychological states and contextual factors in individuals' natural environments (Myin-Germeys et al., 2009), has shown greater success in detecting polygenic interaction effects than cross-sectional self-report approaches (Assary et al., 2018), offering a powerful method to capture the dynamic GxPxE interplay as it unfolds in daily life. In fact, studies using ESM have already shown the impact of daily-stress appraisals in schizotypy traits, subclinical and clinical experiences (e.g., Myn-Germeys et al., 2003; Barrantes-Vidal et al., 2013; Chun et al., 2017; Kwapil et al., 2020; Monsonet et al., 2022). Increasing G×E evidence has also supported the impact of day-to-day experiences across the extended psychosis phenotype (e.g., 2014; Cristobal-Narvaez et al., 2016; Pries et al., 2020; Schick et al., 2022). Notably, a recent proof-of-concept study provided the first evidence that genetic differential susceptibility predicts psychotic-like and affective reactivity to momentary contexts in daily life (Barrantes-Vidal et al., 2025).

AIMS AND OUTLINE

3. AIMS AND OUTLINE

The overarching aim of this thesis is to examine and test the best model fitting gene-environment interactions by using polygenic scores indexing environmental sensitivity and liability to psychiatric disorders, a comprehensive exposome approach to the assessment of early psychosocial experiences, and a transdiagnostic perspective encompassing multiple domains of subclinical psychopathology and positive mental health. The general hypothesis of this thesis is that a substantial proportion of G×E interactions will fit the Differential Susceptibility (DS) model, especially for psychopathology dimensions closely related to stress-sensitivity and for wellbeing indicators. The work presented in this thesis is embedded in the Barcelona Longitudinal Investigation of Schizotypy Study 2 (BLISS-II), a study examining risk and resilience factors across the extended psychosis phenotype (Barrantes-Vidal et al., 2013a; Barrantes-Vidal & Kwapil, 2025). Key findings are further examined in the TwinssCan cohort, a general population twin cohort of adolescents and young adults recruited from the East Flanders Prospective Twin Survey in Belgium (Pries et al., 2017).

The specific goals are the following:

1) To develop a comprehensive early psychosocial exposome integrating both adverse and positive early life experiences, and to examine the associations between the resulting exposome factor and its specific dimensions with subclinical psychopathology, positive mental health and functioning.
2) To develop a methodological workflow that integrates multiple imputation with competitive-confirmatory G×E modeling to enable robust estimation of gene-environment interactions in the presence of missing data.
3) To examine whether genetic sensitivity to the environment moderates the associations between early psychosocial exposome dimensions and subclinical expressions of psychosis, depression, and anxiety, as well as positive mental health indicators, following a DS pattern.
4) To replicate the above DS findings in a general population twin cohort (TwinssCan), by examining interactions between genetic sensitivity to the environment and positive and negative early exposures on subclinical psychosis
5) To examine whether genetic liability to specific psychiatric disorders (i.e., schizophrenia, bipolar disorder, shared liability for schizophrenia and bipolar disorder, and major depressive disorder), moderates the impact of early adverse and positive experiences on transdiagnostic outcomes in a DS manner.
6) To develop and qualitatively evaluate a new set of Experience Sampling Methodology (ESM) items designed to assess momentary sensitivity to contextual and social environmental factors in daily life, using focus groups and cognitive interviewing across clinical and non-clinical populations.

These specific goals were addressed by six empirical studies organized in three main sections.

The **first section** comprises two methodological studies (Chapters 1 and 2) addressing goals 1 and 2 and lays the groundwork for the measurement and analytical approaches

underpinning the empirical work presented throughout the thesis. **Chapter 1** presents the development of a comprehensive early psychosocial exposome model integrating both adverse and positive childhood experiences across multiple domains in a large nonclinical sample. Iterative exploratory factor analyses were conducted to optimize the modeling of environmental variables, and a bifactor confirmatory factor analysis was applied to derive a general exposome score as well as specific factors. **Chapter 2** introduces and illustrates the competitive-confirmatory framework for testing G×E interactions using the LEGIT R package, and provides a systematic workflow integrating multiple imputation via the MICE R package to address the challenge of missing data in G×E research.

The **second section**, pursuing goals 3 to 5, comprises three empirical studies testing the DS model across two independent nonclinical samples. **Chapter 3** presents the first study testing whether a polygenic score for sensitivity to the environment (PGS-ES) moderated the associations between early adverse and positive experiences and a broad range of outcomes including a transdiagnostic psychopathology factor encompassing subclinical psychosis, depression and anxiety, as well as positive mental health and functioning. Consistent with DS, it was hypothesized that individuals with high genetic sensitivity would show increased psychopathology and impaired functioning under adversity but, critically, would also display better outcomes than their less sensitive counterparts under positive or low-adversity conditions. **Chapter 4** aimed at replicating these findings in the TwinssCan general population twin cohort, providing an independent test of the DS model across subclinical expressions of the psychosis continuum, internalizing psychopathology, functioning, and wellbeing. **Chapter 5** further extends this line of research within the TwinssCan cohort by testing whether genetic liability to specific psychiatric disorders (i.e., schizophrenia, bipolar disorder, shared liability for schizophrenia and bipolar disorder, and major depressive disorder) also moderated the impact of early adverse and positive experiences on transdiagnostic outcomes in a DS manner. It was hypothesized that individuals with higher disorder-related polygenic scores would show worse outcomes under adversity but would also display better outcomes, than individuals with lower scores, under positive or low-adversity contexts, consistent with a DS pattern. The **third section**, pursuing goal 6, addresses future directions in the ecological assessment of DS. In this section, **Chapter 6** presents a methodological study aimed at developing and qualitatively evaluating a new set of ESM items to assess momentary sensitivity to contextual and social environmental factors in daily life. Items were developed by adapting existing measures and creating new ones suited for real-time ecological assessment and were evaluated through focus groups combining cognitive interviewing techniques with both clinical and nonclinical participants, with a particular focus on individuals from the psychosis spectrum.

Note. Please note that all studies included in this thesis are presented in article format as they are published (studies from chapter 1, 3 and 4), submitted (study from chapter 6) or to be submitted (studies from chapters 2 and 5) in scientific journals. Thus, reference style and format of the articles varies according to the journal's requirements.

EMPIRICAL WORK

SECTION 1

METHODOLOGICAL ADVANCEMENTS FOR G×E RESEARCH

Chapter 1

Integration of Positive Environmental Factors and Differentiation of Parental Figures in Social Exposome Research

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Abstract

Background: Early adversity is well established as a risk factor for poor mental health, but the potential protective role of positive experiences has been scarcely examined. The exposome paradigm provides a comprehensive framework to model the full spectrum of early environmental experiences, capturing both general and specific dimensions of these experiences. This study aimed to (i) develop an Early Social Exposome score integrating positive and negative experiences, and (ii) explore its associations with positive and negative outcomes.
Methods: Early environmental experiences, psychopathology, positive outcomes, and functioning were assessed for 1181 non-clinical young adults. Iterative exploratory factor analyses were conducted to optimize the modeling of environmental variables. A final Bifactor Confirmatory Factor Analysis was applied to obtain factor scores.
Results: A general score and four specific factors emerged: Positive Experiences, Paternal Adversity, Maternal Adversity, and Role Reversal. The general Early Exposome was associated with higher psychopathology and lower positive mental health and functioning, whereas Positive Experiences showed the opposite pattern. Maternal Adversity was associated with psychopathology, whereas Paternal Adversity, mirroring epidemiological findings, showed a modest relationship with poorer functioning.
Conclusions: Findings highlight the importance of assessing and integrating positive experiences in exposome research when modeling the early social environment. Its inclusion allowed to capture the significant protective role of positive peer experiences, which probably partially accounts for the heterogeneity of outcomes related to adversity exposures. Additionally, the figure or source of childhood experiences emerged as a relevant factor that should be contemplated in future research along with the nature of experiences.

1. Introduction

Early childhood is a critical period marked by heightened sensitivity to environmental influences. These formative years encapsulate a diverse spectrum of experiences that have profound and enduring effects on mental health (Shonkoff and Phillips, 2000). This malleability to environmental inputs is driven by rapid neurodevelopment and increased brain plasticity that characterizes this sensitive period (Kolb et al., 2013).

Adverse Childhood Experiences (ACE) can alter brain development, influencing neural circuits involved in threat detection, emotional regulation and reward processing (Teicher et al., 2016; Samson et al., 2024) and have long-lasting effects on psychological and social functioning (Pfaltz et al., 2022; Sheinbaum et al., 2024; Heinonen et al., 2018). ACE are associated with increased risk for many psychopathology expressions (Hostinar et al., 2023; McLaughlin et al., 2020; Pietrek et al., 2013), including depression (Humphreys et al., 2020), anxiety (Bandoli et al., 2017), behavioral disorders (Ballard et al., 2015) and psychosis (Sideli et al., 2020; Catalan et al., 2017). The high comorbidity rates across mental health disorders (McGrath et al., 2020) led to the identification of a broad, superordinate factor of general psychopathology (Snyder and Hankin, 2017; Smith et al., 2020), often called the P-factor (Caspi et al., 2014). This concept suggests a common dimension contributing to the interconnectedness of mental health symptoms and facilitates the examination of common risk and protective factors across diagnostic categories (Carver et al., 2017). However, whether a single dimension can capture the complexity and diversity of psychopathological variation is debated (Watts et al., 2024).

In contrast to ACE, research has scarcely examined the role of positive childhood experiences (PCE; e.g., supportive relationships, safe environments) in shaping mental health outcomes (Narayan et al., 2018; Masten, 2006). PCE not only buffer the detrimental impact of ACE, fostering resilience and well-being (Bethell et al., 2019; Redican et al., 2023), but independently contribute to improved adult health and reduced risk of mental and physical infirmity (Huang et al., 2023).

The operationalization and empirical study of early environments have largely focused on adversity (Lacey and Minnis, 2020). *Specificity models* focus on the individual effects of specific adversities (Cecil et al., 2017), whereas the *cumulative risk* models posit that multiple adversities have additive effects on developmental outcomes (Evans, Li and Whipple, 2013). Both approaches have limitations: specificity models fail to account for interplay and co-occurrence of individual adversities, whereas cumulative risk approaches lack precision in detailing mechanisms through which adversities influence development (McLaughlin et al., 2021).

Dimensional models have emerged as an alternative and encompass theory-driven and empirically-driven methods (Lacey and Minnis, 2020). Theory-driven models, such as the Dimensional Model of Adversity and Psychopathology (McLaughlin and Sheridan, 2016), aim to identify core underlying dimensions across types of adversities likely affecting developmental processes similarly (McLaughlin et al., 2021). Though gaining empirical support (e.g., Miller et al., 2018; Schäfer et al., 2023), this approach also has limitations, as some adversity subtypes do not fit into these dimensions or overlap across categories (Smith and Pollak, 2021). Empirically-driven methods, like factor analysis, group adversities based on correlations to derive dimensions (Lacey and Minnis, 2020) and offer explanatory power in investigating associations with several

phenotypes (Brumley et al., 2019). Recent research supports combining approaches, revealing that different early experiences seem to specifically influence certain developmental processes, while also contributing to a general and cumulative vulnerability that impacts the expression of psychopathology (McGinnis et al., 2022; Gizdic et al., 2023).

Recently, the exposome paradigm has gained prominence in epidemiological research. This innovative approach advocates for the comprehensive integration of all environmental exposures experienced across a lifetime (Wild, 2005; Guloksuz et al., 2018). Exposome scores— aggregate weighted scores of environmental exposures—predict general mental health and functioning (Erzin and Guloksuz, 2021; Moore et al., 2022; Barzilay et al., 2022; Pries et al., 2022). Apart from this overarching score, the exposome framework also accounts for the specificity of environmental subdomains, and specific factors comprising the exposome have also been modeled (Pries et al., 2022).

While advances in exposome research have significantly improved our understanding of environmental exposures and their health effects—for instance, through major initiatives that map complex environmental exposures across the lifespan (HELIX Project, ISGlobal, 2020; CityExposomeCat, ISGlobal, 2021)—much of this work has focused on biological (e.g., endocrine disruptors, Warkentin et al., 2025), chemical (e.g., air pollution, Dominguez et al., 2025), and physical exposures (e.g., urban environment studies, Khomenko et al., 2025), leaving social and structural factors underrepresented (Gudi-Mindermann et al., 2023). Moreover, exposome research lacks studies examining both positive and negative experiences. Assessing positive experiences allows studying their potential role fostering resilience and favorable outcomes (Thakkar et al., 2023) and may better account for heterogenous outcomes associated with adversity.

The present study

This study employs an exposome framework analysis (Moore et al., 2022; Guloksuz et al., 2018) integrating a wide range of *both* adverse and positive early experiences. Furthermore, the study explores the associations of the early social exposome and its dimensions with both subclinical trans-syndromic psychopathology dimensions and positive mental health outcomes.

The study has two specific goals. First, to develop a comprehensive early exposome factor integrating adverse and positive experiences. Following Moore et al. (2022), we employed iterative factor analyses aimed at optimizing data dimensionality and tested the goodness of fit of a bifactor model encompassing both a general factor (i.e., exposome) and specific factors. Second, we examined the associations between the derived early exposome factor and its dimensions with three outcome domains—subclinical psychopathology, positive mental health, and general and social functioning.

Note that the exploratory nature of the analyses precluded making specific hypotheses regarding the number and content of the factor analysis-derived dimensions. However, we expected that elevated levels of adversity, as reflected in the general factor, would be associated with more symptoms, worse functioning, and lower levels of positive mental health, whereas higher levels of positive experiences would be related to fewer symptoms, enhanced functioning, and greater positive mental health indicators.

2. Methods

2.1. Participants

The study sample was composed of 1181 non-clinically ascertained young adults (*M* age = 22.8 years, *SD* = 6.5, range = 18-62 years, 76% female) recruited from two universities in Barcelona. Breakdown of socioeconomic status was 3% low, 10.8% middle-low, 31.5% middle class, 61.2% middle-high, and 3.5% high. Initially, 1220 participants completed the measures; however, 39 participants were excluded due to invalid responding, defined by a score greater than 3 on the Infrequency Scale (Chapman and Chapman, 1983). Recruitment was conducted via posters and emails sent to students and university staff and took place between 16 December 2022 and 29 March 2023. Exclusion criteria included: a) being under 18 years old, and b) having grandparents of non-Spanish origin to maintain ancestry homogeneity for genetic analyses used in the project. Written informed consent was obtained from all participants. The study was approved (ref. 5426) by the Ethics Committee of the Universitat Autònoma de Barcelona (Comissió d'Ètica en l'Experimentació Animal i Humana).

2.2. Materials and procedure

See Supplementary Material for a detailed description of the measures.

2.2.1. Environmental measures

A total of 145 items reflecting a multidimensional exploration of early social environment were included in the analysis. These variables encompass positive and negative experiences from early childhood, including school dynamics, intrafamilial relationships, peer interactions, neighborhood characteristics, and financial status. The items were drawn from established self-report scales, including the Childhood Trauma Questionnaire-Brief (Bernstein et al., 2003), the Childhood Experiences of Care and Abuse Questionnaire-3 Brief (Li et al., 2020), the Parental Bonding Instrument (PBI; Parker et al., 1979), the Benevolent Childhood Experiences Scale (Narayan et al., 2018), the Positive Childhood Experiences Scale (Bethell et al., 2019) and 4 items assessing family-level protective factors derived by Crush et al. (2018).

2.2.2. Phenotypic measures

Schizotypy traits and experiences were assessed with the Multidimensional Schizotypy Scale-Brief (MSS-B; Gross et al., 2018), the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) and the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002). Depressive symptoms with the Beck Depression Inventory (BDI; Beck et al., 1979) and anxiety with the Beck Anxiety Inventory (BAI; Beck et al., 1988).

Positive mental health was assessed using the Rosenberg Self-Esteem Scale (Rosenberg, 1965), the Connor-Davidson Resilience Scale (Campbell-Sills and Stein, 2007) and the Warwick-Edinburgh Mental Wellbeing Scale (Tennant et al., 2007).

Functioning was assessed with the Social Functioning Questionnaire (Tyrer et al., 2005).

2.3 Statistical analysis

2.3.1 Modeling of early environment and generation of factor scores

All 145 items from the early environmental measures were included in the analysis (Table S1). Given the large number of variables, diverse formats (ordinal, continuous, and binary), and

the data's multidimensional yet interconnected nature, a complex data reduction process was conducted following Moore et al. (2022). Subsequently, the underlying factorial structure of the remaining items was entered into a Bifactor Confirmatory Factor Analysis (BCFA). See Supplementary Methods for a detailed description of the process.

2.3.2 *Modeling of psychopathology, positive mental health, and functioning outcome measures and determination of factor scores*

We derived an integrative P-factor score capturing transdiagnostic vulnerability to subclinical psychopathology including psychosis-spectrum, depressive, and anxiety features, as well as an analogous general factor score tapping positive mental health indicators such as well-being, resilience, and self-esteem. For each indicator, an EFA was conducted on all measures comprising it, and the resulting factorial structure was then used in a BCFA to compute a composite score.

2.3.3 Associations of Early Exposome factor scores with outcome variables

Bivariate correlations and linear regression analysis were computed to test the association of the Early Exposome and its dimensions with the P-factor, Positive Mental Health index, functioning, and individual measures of psychopathology and positive mental health. In the regression analysis all predictors were entered simultaneously to examine their unique contribution. Bootstrap procedures with 2000 samples were used for regression models. The standardized regression coefficients (β) and effect sizes (f^2) are reported for each predictor in the linear regressions.

3. Results

3.1. Results of the environmental data reduction

Descriptive statistics, reliability and correlations for study variables are displayed in Tables S2 and S3. A total of five EFAs were conducted (Tables S4-S7; Table 1) until a final solution was obtained, retaining 99 of the initial 145 variables for subsequent analysis. All items were included in the initial EFA (Table S4). Items from measures that separate the mother/father figure clustered together within the same factors, whereas general items that did not specify parental figures grouped similarly. This prompted running two EFAs to analyze these two sets of items independently (Tables S5-S6) and then we conducted a fourth EFA (Table S7) including all remaining items and subscales from all measures.

The concluding EFA employing iterated target rotation (ITR; Moore et al., 2015) revealed a four-factor solution (Table 1), as indicated by the scree plot in Figure S1. Factor 1 encompassed extra-familiar positive experiences and peer support ("Positive Experiences"). Factor 2 included negative experiences or lack of care related to the paternal figure ("Paternal Adversity"). Factor 3 covered similar experiences as Factor 2 but pertaining to the maternal figure ("Maternal Adversity"). Factor 4 (“Role Reversal”) included items related to role reversal and some low-endorsed items related to other adverse experiences, such as parental violence and physical neglect.

The subsequent BCFA (see Figure 1 and Table S8) demonstrated good global fit (CFI = .97, TLI = .97, SRMR = .06, and RMSEA = .05). All factors exhibited high reliability (ω = .86 - .96; H = .90 - .98). Table S9 shows the complete model-based reliability results.

The general factor accounted for 56.7% of the ECV, indicating a strong general factor while also suggesting multidimensionality. Specific factors exhibited varying proportions of ECV, lower than the general factor (mean ECV-SG of 10.83% (range: 6.1% - 14.9%)), representing a contribution to the model in terms of explaining specific aspects or subdomains within the broader construct measured by the general factor.

3.2. Derivation of a P-factor score

An EFA using ITR revealed a four-factor structure with some cross-loadings (Table S11). The subsequent BCFA (Table S12) presented good model fit (CFI = .95, TLI = .94, RMSEA = .047, SRMR = .066; Table S13 shows additional bifactor fit indices). A general P-factor plus four distinct factors were identified: Affective Dysregulation, Social/Cognitive Malfunctioning, Positive Schizotypy, and Negative Schizotypy.

3.3. Derivation of a Positive Mental Health Index

Given the expectation of a simple structure, an EFA with oblimin rotation was conducted. Items clustered by measure, yielding a three-factor solution devoid of cross-loadings (Table S13). The subsequent BCFA (Table S14) exhibited excellent fit (CFI = .97; TLI = .97; SRMR = .044; RMSEA = .087; Table S15 shows additional bifactor fit indices).

3.4. Associations of the Early Exposome and its dimensions with outcome domains and individual scales

Table 2 presents the linear regression analyses examining the Early Exposome and its dimensions as predictors of the P-factor, the Positive Mental Health index and functioning, as well as the individual psychopathology and positive mental health measures. Bivariate correlations are presented in Tables S16 and S17.

The total effects of the model, including the general and specific factors as predictors, were significantly associated with all primary outcome domains. Effect sizes were moderate for the P-factor and Positive Mental Health Index, whereas the effect size was large for functioning.

The general factor (moderate effect size) and Positive Experiences (small effect) were significantly associated with all outcome domains in the expected direction. Maternal Adversity showed a small but significant association with the P-factor, Paternal Adversity with functioning, and Role Reversal with the Positive Mental Health index—driven by an association with resilience; however, the last two did not reach the small effect size criterion.

At the individual scale level, the total effects of the model showed positive associations of moderate effect size with disorganized schizotypy, suspiciousness, depression, well-being, and self-esteem. These effects were primarily driven by the general factor, which also demonstrated small to moderate effect size associations for the same outcomes.

Significant inverse associations were found for Positive Experiences with negative and disorganized schizotypy, suspiciousness, and depression, as well as positive associations with well-being, resilience and self-esteem (small effect sizes). Paternal Adversity presented a small negative association with resilience, Maternal Adversity showed a small positive association with negative and disorganized schizotypy, and Role Reversal exhibited a positive correlation with positive schizotypy and resilience.

The model explained 22% of the variance in the P-factor, 17.3% in Positive Mental Health, and 29.1% in functioning. For the individual scales, it explained between 4.6% and 20.4% of the variance in psychopathology symptoms and between 11.4% and 18.7% for the positive mental health indicators. Correlations were closely comparable for the analogous regression analyses of the Early Exposome and its specific dimensions with both outcome domains and individual measures.

4. Discussion

To our knowledge, this is the first investigation integrating both positive and adverse early experiences within a multifactorial exposome framework and testing their impact not only on psychopathology, but also on positive mental health outcomes and functioning. The bifactor model applied revealed a general factor and four specific factors: Positive Experiences, Paternal Adversity, Maternal Adversity and Role Reversal, which presented distinct patterns of associations with psychopathology, well-being and functioning. While the general factor captured the overarching negative impact of adversity on all psychological outcomes, Positive Experiences emerged as a robust predictor of improved well-being and as a protective factor against psychopathology, highlighting the critical importance of peer and social support during formative years. Importantly, experiences of maternal adversity showed a negative impact on individuals' psychopathology, whereas paternal adversity was slightly related to poorer functioning. Overall, these findings underscore the intricate nature of early environmental influences, illustrating that the dynamic interplay between negative and positive experiences originating from diverse figures plays a pivotal role in shaping pathways of risk and resilience during early development.

4.1. Modelling early experiences

Unlike dimensional adversity models, that differentiate by the type of experience (e.g., threat or deprivation; McLaughlin and Sheridan, 2016), our analyses revealed separate dimensions for paternal and maternal adversity. Therefore, it seems that grouping experiences by the source of adversity in combination with the nature may allow for a better understanding of how different relational contexts influence developmental outcomes. This finding reflects the complexity of early environmental influences and the potential co-existing roles of different figures in a child's life (e.g., one parent may be a source of adversity, while the other may provide protection). This aligns with evidence that mothers and fathers often play distinct roles in child's development, reflecting unique patterns of caregiving and adversity. Research suggests that within a family unit, fathers are often more involved in a child's social development (Yaacob, 2006), whereas mothers frequently assume the primary caregiving role (Bornstein et al., 2018). This translates into more time spent with children (Cui et al., 2018), which increases the likelihood of mothers being involved in conflicts with their offspring (Bornstein, 2007) and results in a more direct exposure to maternal stress or adversity (Gryczkowski et al., 2010). The predominance of female participants in our sample (76%) might also be relevant to interpreting broader gender-based differences in parenting dynamics (although the study still included nearly 300 male participants). For example, maternal adversity has been shown to exert a stronger influence on psychopathology in female offspring, whereas paternal adversity has a greater impact on males (Oshio and Umeda, 2016). Similarly, research has found that children's behaviors often correlate more strongly with

the parenting style of the same-gender parent (Hoeve et al., 2011; Long et al., 2018). It is relevant to note that most factor-analytic research has not included measures that distinguish maternal and paternal behaviors (e.g., PBI), which may account for the lack of differentiation of these figure-related factors in other studies. Our results, concurrent with longstanding clinical observations, suggest that the differentiation of maternal and paternal caregiving (or other caregiving configurations in contemporary society) provides a more accurate understanding of early relational contexts and how these dynamics uniquely shape psychological outcomes. However, further research with more gender-balanced samples is necessary to confirm and extend these findings.

4.2. Associations between the Early Exposome and psychopathology, positive mental health and functioning.

As expected, the general exposome factor—reflecting adversity—was associated with elevations in all psychopathology measures as well as diminished positive mental health and functioning. This trans-syndromic effect indicates broad, undifferentiated effects, as expected from an overarching score. The strongest association was with decreased functioning followed by lower well-being and depressive symptoms. These findings support the predictive value of scores capturing early adversities' cumulative effects in forecasting the risks of various psychopathological outcomes (Morgan et al., 2020; Khan et al., 2022), functioning (McGinnis et al., 2022) and positive mental health indicators (Keinan et al., 2012). Additionally, this approach refines traditional cumulative scores, as modeling latent dimensions into factors has been shown to yield more accurate predictions (Brumley et al., 2019; Gizdic et al., 2023).

Positive Experiences was associated with better positive mental health and showed a large inverse association with functioning and trans-syndromic psychopathology. The nature of our sample—primarily college students with relatively low trauma exposure and possibly a higher range positive experiences—might have contributed to stronger effects for this factor compared to others. This factor comprised both peer and family experiences; however, family-related items (e.g., “My family was a source of strength and help”), lost prominence as they loaded higher onto the general score. Thus, Positive Experiences predominantly reflected variance related to peer support, especially in school contexts. These findings align with developmental research on the significance of peer relationships in late childhood and adolescence (e.g., Wang and Hu, 2021), school connectedness (Goetschius et al., 2023), and close friendships (Ku et al., 2024). Furthermore, Positive Experiences included emotional support items (e.g., “I felt loved”), highlighting the strong connection between social networks and feeling emotionally supported. This aligns with a longitudinal study by Sheinbaum et al. (2024) reporting emotional neglect to be associated with loneliness and lower social support. This may also explain the inverse association of Positive Experiences with negative psychotic symptoms, as neglect has been consistently associated with negative features over and above other adversity dimensions (Alameda et al., 2021; Bailey et al., 2018).

The Paternal and Maternal Adversity factors included inverse loadings of some positive experiences (items from the PBI care subscale) but were predominantly characterized by adversity (antipathy, psychological abuse, overprotection). Notably, Maternal Adversity included more severe items absent in Paternal Adversity (e.g., "Said she wanted me dead", "Deprived me of light, food or company") and was more heavily loaded with negative items, whereas Paternal Adversity

included more positive items. This may have influenced the detection of associations with psychopathology but not positive mental health. These findings align with studies showing maternal adversity, including maternal alcohol abuse (Long et al., 2018) or mental disorders (Shih et al., 2023; Pilowski et al., 2014) has a greater impact on offspring psychopathology (including anxiety, depression, and other behavioral issues) than paternal adversity. Conversely, Paternal Adversity was associated with poorer functioning, consistent with studies suggesting fathers' predominant role in social development, social status, and skills (Leidy et al., 2013; Feldman, 2023), and showed a slight positive association with resilience, supporting evidence that father involvement in caregiving fosters resilience in children's development (Feldman, 2023).

Role Reversal was not associated with the main outcome domains and showed the fewest associations with individual measures, likely because, apart from role reversal items, this factor included low-endorsed items of parental violence and physical neglect, representing severe adversity. Interestingly, it showed a small positive association with resilience, which might be related to the premature adoption of adult roles—problem-solving, coping with difficulties, and resolving the dissonance of becoming the caretaker—and aligns with the potential positive outcomes of distress through resilience, as conceptualized by post-traumatic growth (Black & Wright, 2012), a term describing positive psychological adaptations after overcoming challenging situations (Kadri et al., 2025).

Effect sizes were larger for the general factor than for the specific factors, as expected in bifactor models, where the general factor absorbs much of the shared variance across items and the specific factors reflect residual, highly specific variance. As a result, their correlations with external outcomes are constrained, yielding smaller effect sizes. Alternative models, like the correlated traits model applied to exposome subdomains by Pries et al. (2022), distribute variance differently, often producing stronger associations. In this approach, item variance is fully allocated to each factor and factors can correlate, capturing both within- and between-factor variance. While this can increase effect sizes, it reduces interpretability because nonspecific variance is included in each factor (Reise, 2012). In contrast, the smaller associations for specific factors in our bifactor model are statistically significant and theoretically meaningful, revealing what each construct contributes beyond the general factor—a central aim of our study. Both approaches have trade-offs, and model choice depends on research goals (Henry et al., 2021). In our case, the bifactor model provides a clearer test of cumulative versus domain-specific influences. More broadly, these trade-offs underscore the need for further research on balancing specificity and generality in modeling complex phenomena like early experiences.

4.3. Challenges in the operationalization of positive and negative experiences

Despite efforts to include a substantial number of items capturing positive experiences, the higher proportion of negative items (60 negative vs. 39 positive) likely drove the direction of the general factor towards adversity (Fabrigar and Wegener, 2012), with positive items loading inversely on this factor. Consequently, the Early Exposome scores do not have a bipolar nature but rather indicate the presence and absence of adversity across a unipolar dimension. A relevant example to consider the validity of this commonly used approach is that of positive and negative affect. These two valences are typically conceptualized as separate dimensions rather than opposite ends of a single spectrum (Watson et al., 1988). Similarly, it might be argued that decreasing the

score of negative environmental experiences due to the existence of positive ones is not a proper way of modelling them, as it is well-established that they can be experienced simultaneously and separately, and the effect of positive experiences probably extends beyond compensating the level of adversity experienced. In this regard, methodologies such as cluster or latent class analysis could help identify unique profiles of early experiences, revealing distinct patterns of adversity and resilience that inform our understanding of individual developmental trajectories.

4.4. Strengths and limitations

A key strength of this study is the assessment of a wide range of positive and negative early life experiences—as well as the trans-syndromic approach to examine their impact on psychopathology—in a large sample of young adults. Studying young adults is particularly suited for examining these associations, as this developmental stage marks a peak period for the onset of psychopathology and offers key prevention opportunities (Cicchetti, 2023). Unlike most studies focusing primarily on symptoms, we also examined functioning and positive mental health outcomes. Furthermore, bifactor modeling of early experiences provides a novel operationalization that reduces the divide between cumulative and specificity approaches by capturing fine-grained variance within specific factors and item-level associations reflecting commonalities of early experiences.

A limitation is the cross-sectional design and reliance on retrospective self-reports to assess early experiences. However, concerns about self-report reliability have been challenged by evidence showing high corroboration rates for abuse reports, even among psychiatric patients (74–82%; Read et al., 2005) and research suggests interview-based methods are not inherently more valid or reliable than self-reports (Linscott and van Os, 2013). While the social environment cannot be reduced to single aspects (Gudi-Mindermann et al., 2023), we focused on social interactions as they connect the individual to the external world and play a fundamental role in health and development. In line with Colomina et al. (2018), we emphasize psychosocial environmental exposures, particularly early life experiences that shape neural circuits and influence susceptibility to environmental factors. However, future research should expand to other social dimensions, such as socioeconomic circumstances and sociodemographic characteristics.

The sample, composed of young adults with mostly middle-to-high socioeconomic status (64.7%) from two universities in Barcelona and an overrepresentation of women—a common challenge in voluntary participation as women are generally more likely to volunteer (Lobato et al., 2014)—may limit generalizability. Nevertheless, the study included a substantial number of male participants. Our findings provide insights into source-specific environmental factors; however, given the exploratory nature and sample composition, replication in more diverse populations is needed to further confirm the factorial structure and associations, as the restricted sample may attenuate effects due to limited range.

5. Conclusions

Our findings underscore the need to develop and incorporate measures that capture the full spectrum of environmental experiences, adverse and positive. Acknowledging the coexistence and dynamic interplay of supportive and adverse experiences will help to better understand the pathways of risk and resilience to mental health and will probably partially account for the heterogeneity of outcomes related to adversity exposures (McLaughlin and Gabard-Durnam,

2022). Results also highlight the importance of assessing different relational contexts (including relationships with peers and parental figures) in the study of environmental factors. Overall, accounting for the multifaceted realities of early development is crucial to inform preventive interventions and clinical practices aimed at promoting resilience and well-being in individuals who have faced childhood adversity.

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Tables and Figures

Table 1. Factor loadings of the final exploratory factor analysis of the optimized collection of Early Exposome items using iterative target rotation (n = 1.181).

Item	Content	FAC1 Positive Experiences	FAC2 Paternal Aversity	FAC3 Maternal Adversity	FAC4 Role Reversal
PCE4_R	Sense of belonging in high school	**0.97**	0.19	0.25	0.09
BCE_8	Opportunities to have a good time	**0.92**	0.07	0.35	-0.04
PCE5_R	Felt supported by friends	**0.91**	0.13	0.32	0.08
Support2R	Peers to discuss problems and feelings	**0.89**	0.10	0.35	0.09
BCE2_R	At least one good friend	**0.87**	0.18	0.33	0.07
BCE_42R	Liked high school	**0.86**	0.12	0.28	0.06
PCE3_R	Enjoyed community traditions	**0.79**	-0.02	0.15	0.02
BCE7_R	Adult who provided support or advice	**0.70**	0.01	0.14	0.06
PCE7_R	Felt safe and protected by an adult at home	**0.68**	-0.08	-0.03	-0.23
PCE1_R	Capable of discussing feelings with family	**0.68**	-0.05	-0.06	0.12
PCE2_R	Supported by family during tough times	**0.68**	-0.05	-0.13	0.01
BCE5_R	At least one teacher that cared	**0.67**	0.00	0.30	0.06
BCE_9	Like or felt comfortable with oneself	**0.66**	0.00	0.13	-0.04
CTQ_7	Felt loved	**0.62**	-0.19	-0.13	-0.11
PCE6_R	At least two caring adults (not parents)	**0.62**	-0.07	0.07	-0.03
BCE_41R	Liked school	**0.59**	-0.02	0.19	-0.06
CTQ_5	Family member made me feel valued	**0.58**	-0.07	-0.17	0.07
CTQ_2	Family member took care of me	**0.58**	-0.04	0.01	-0.23
BCE1_R	Caregiver provided sense of safety	**0.56**	-0.04	0.06	0.02
FAMILYPROT2	Ways to have fun at home	**0.51**	-0.19	-0.02	-0.26
CTQ_29	Family was source of strength	**0.49**	-0.23	-0.18	-0.17
Support1R	Adults could go to with problems/discuss feelings	**0.49**	-0.16	-0.19	0.02
CTQ_20	Family felt close	**0.44**	-0.21	-0.04	-0.22
FAMILYPROT3	Lived in a happy home	**0.40**	-0.29	-0.05	-0.37
CARE_P1	Spoke in a warm and friendly voice	0.11	**-0.79**	0.04	0.02
PA_P4	Humiliated me, put me down.	-0.02	**0.78**	0.04	0.16
ANTIPATHY_F2	Was critical of me	-0.17	**0.77**	0.00	-0.01
ANTIPATHY_F1	Was difficult to please	-0.12	**0.75**	0.02	0.03
PA_P6	Was rejecting	-0.05	**0.74**	0.11	0.10
ANTIPATHY_F3	Made me feel I was a nuisance	-0.11	**0.74**	0.05	0.12
CARE_P5	Enjoyed talking things over with me	0.15	**-0.73**	-0.04	0.16
CARE_P6	Frequently smiled at me	0.10	**-0.72**	-0.09	0.10
PA_P1	Undermined my confidence	-0.06	**0.71**	0.00	0.08
PA_P2	Played on my fears	0.00	**0.69**	0.07	0.16
ANTIPATHY_F4	Picked on me unfairly	-0.08	**0.69**	-0.02	0.15
CARE_P9	Emotionally cold to me	-0.13	**0.69**	0.11	-0.11
PA_P8	Made me feel guilty, so I would do what I was told	0.16	**0.68**	0.12	0.29
CARE_P11	Made me feel I wasn't wanted	-0.22	**0.67**	-0.04	0.02
CARE_P4	Was affectionate to me	0.12	**-0.67**	-0.09	0.09
CARE_P12	Did not praise me	-0.22	**0.66**	0.06	-0.16
CARE_P8	Did not talk with me very much	-0.13	**0.66**	0.10	-0.13
CARE_P10	Did not understand what I needed or wanted	-0.23	**0.65**	0.06	0.00
CARE_P3	Understood my problems and worries	0.23	**-0.64**	-0.04	0.08
PA_P3	Liked to see me suffer	-0.13	**0.63**	-0.07	0.12
CARE_P7	Made me feel better when I was upset	0.15	**-0.62**	-0.04	0.07
PA_P7	Took away things I cherished	-0.09	**0.57**	0.04	0.17
PA_P5	Shamed me in front of others	-0.06	**0.54**	0.06	0.11
PBI_Fat_OVERPR	Subscale score	0.02	**0.49**	0.09	0.05
ANTIPATHY_F6	Did not like me as much as my siblings	-0.24	**0.45**	0.07	-0.10
CARE_P2	Did not help me as much as I needed	-0.23	**0.45**	0.09	-0.02
ANTIPATHY_F5	Was there if I needed	-0.19	**0.32**	-0.09	-0.08
ANTIPATHY_M3	Was critical	-0.03	-0.01	**0.82**	0.08

ANTIPATHY_M1	Was difficult to please	-0.05	0.05	**0.74**	0.07
ANTIPATHY_M4	Made me feel I was a nuisance	-0.07	0.06	**0.74**	0.19
PA_M4	Humiliated me, put me down	0.02	0.02	**0.74**	0.20
PA_M1	Undermined my confidence	0.04	0.13	**0.73**	0.03
ANTIPATHY_M5	Picked on me unfairly	0.03	-0.07	**0.70**	0.25
CARE_M5	Enjoyed talking things over with me	0.18	-0.01	**-0.69**	0.11
CARE_M1	Spoke in a warm and friendly voice	0.15	0.01	**-0.68**	-0.01
PA_M8	Made me feel guilty, so I would do what I was told	0.04	0.06	**0.68**	0.14
CARE_M9	Emotionally cold to me	-0.13	0.00	**0.67**	0.02
PA_M3	Played on my fears	0.00	0.07	**0.67**	0.13
CARE_M11	Made me feel I wasn't wanted	-0.25	-0.02	**0.67**	0.03
ANTIPATHY_M2	Made me feel unwanted	-0.27	-0.13	**0.66**	0.08
PA_M6	Was rejecting	-0.20	-0.05	**0.66**	0.05
CARE_M4	Was affectionate to me	0.16	-0.04	**-0.64**	0.00
CARE_M3	Understood my problems and worries	0.24	-0.01	**-0.64**	0.03
CARE_M10	Did not understand what I needed or wanted	-0.21	0.08	**0.63**	-0.02
CARE_M6	Frequently smiled at me	0.23	-0.01	**-0.60**	0.01
CARE_M12	Did not praise me	-0.23	0.08	**0.59**	-0.09
PA_M2	Confuse me by telling contradictory things	0.00	0.09	**0.56**	0.13
PBI_Mot_OVERPR	Subscale score	0.09	0.17	**0.56**	-0.02
CARE_M8	Did not talk with me very much	-0.24	0.01	**0.56**	-0.07
PA_M5	Shamed me in front of others	-0.05	0.05	**0.54**	0.12
CARE_M7	Made me feel better when I was upset	0.17	0.01	**-0.53**	0.08
PA_M9	Threatened to hurt loved ones to get what she wanted	0.02	-0.26	**0.52**	0.37
ANTIPATHY_M6	Did not like me as much as my siblings	-0.21	-0.04	**0.50**	0.06
PA_M11	Said wanted me dead	-0.23	-0.16	**0.45**	0.38
CARE_M2	Not helped me as much as I needed	-0.22	0.06	**0.42**	0.12
PA_M7	Deprivation of light, food, or company	0.04	0.11	**0.41**	0.37
CTQ_3	Family called me things like "stupid", "lazy" or "ugly"	-0.16	0.27	**0.31**	0.23
RR_5R	Parent/s look to you for help as a child	0.02	-0.04	0.03	**0.61**
RR_1R	Lot of responsibility at home	-0.06	0.04	0.06	**0.59**
CTQ_1	Not enough food to eat	-0.17	-0.04	0.02	**0.58**
RR_6R	Parent/s confided their problems in you	0.13	-0.03	-0.03	**0.58**
RR_9R	Felt concerned and worried about parents	0.00	0.09	-0.04	**0.56**
RR_2R	Expected to do a lot of housework	-0.09	0.02	0.11	**0.51**
CECA_Discord	Subscale score	-0.06	0.22	0.13	**0.51**
CTQ_4	Parents too drunk or to high	-0.10	0.13	-0.12	**0.51**
CTQ_6	Wore dirty clothes	-0.21	-0.11	-0.07	**0.50**
RR_8R	Parent/s rely for emotional support as a child	0.01	0.15	0.15	**0.50**
RR_4R	Missed out seeing friends because of home responsibilities	-0.04	0.09	0.14	**0.48**
BCE10_R	Had a predictable home routine	0.38	-0.01	0.09	**-0.44**
RR_3R	Had to look after younger siblings	0.00	0.04	0.13	**0.43**
CECA_Violence	Subscale score	0.06	0.12	-0.03	**0.43**
FAMILYPROT4	Home overly chaotic or noisy	0.10	-0.13	-0.09	**-0.39**
CTQ_26	Was emotionally abused	-0.21	0.27	0.21	**0.38**
CTQ_14	Family said hurful or insulting things	-0.09	0.32	0.20	**0.37**
CTQ_Physical_Abuse	Subscale score	-0.04	0.17	0.19	**0.33**

	Inter-factor correlations resulting from EFA			
	F1 Positive	F2 Father	F3 Mother	F4 General Adv.
FAC 1	-			
FAC 2	-.52	-		
FAC 3	-.63	.29	-	
FAC 4	-.32	.15	.23	-

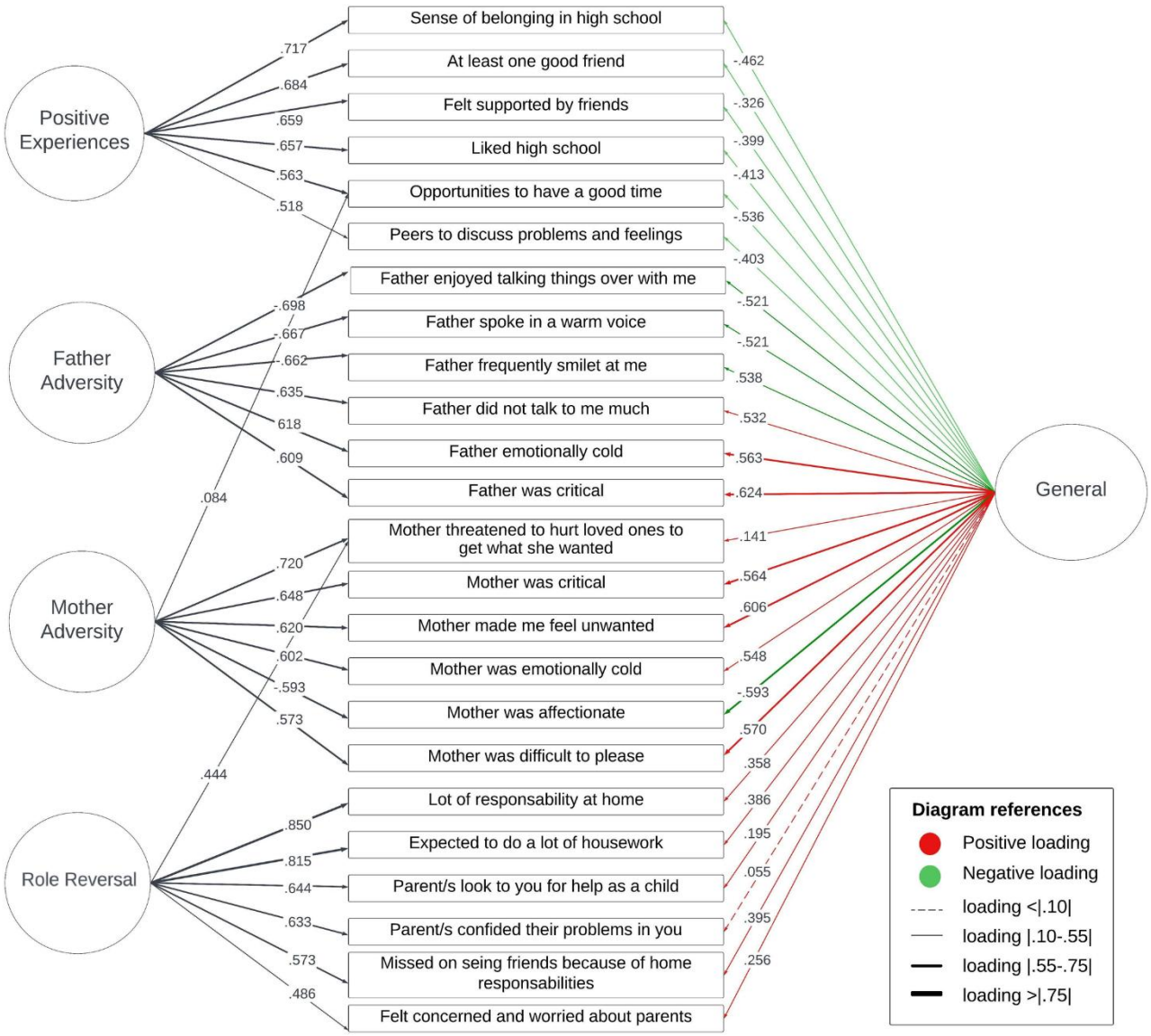
Highest factor loadings for a given factor are bolded; Crossloadings are underlined; CTQ: Childhood Trauma Questionnaire, RR: Role Reversal; CECA: Childhood Experiences of Care and Abuse; PA: Psychological Abuse; PCE: Positive Chlildhood Experiences; BCE: Benevolent Childhood Experiences.

Table 2. Linear regressions examining prediction of the main outcome domains and individual (P-factor, a Positive Mental Health Index and functioning) and individual measures by the Early Exposome and its dimensions (n = 1181).

	Regression Model																	
	Early Exposome			F1 Positive Experiences			F2 Paternal Adversity			F3 Maternal Adversity			F4 Role Reversal			Total effect		
Criteria	β	*p*	f^2	β	*p*	f^2	β	*p*	f^2	β	*p*	f^2	β	*p*	f^2	R^2	*p*	f^2
MAIN OUTCOME DOMAINS																		
P-factor	.401	.000	**.20**	-.171	.000	.04	.043	.097	.00	.100	.000	.01	.041	.113	.00	.220	.000	**.28**
Positive Mental Health	-.367	.000	**.16**	.155	.000	.03	-.022	.417	.00	-.043	.104	.00	.056	.036	.00	.173	.000	**.21**
Functioning	-.484	.000	**.32**	.188	.000	.05	-.062	.013	.01	-.028	.267	.00	.021	.400	.00	.291	.000	***.41***
INDIVIDUAL MEASURES																		
Psychosis Extended Phenotype																		
MSS Positive	.161	.000	.03	-.033	.242	.00	.015	.598	.00	.084	.004	.01	.119	.000	.01	.053	.000	.06
MSS Negative	.222	.000	.05	-.148	.000	.02	-.017	.552	.00	.026	.366	.00	-.002	.946	.00	.075	.000	.08
MSS Disorganized	.341	.000	.13	-141	.000	.02	.037	.171	.00	.096	.000	.01	.020	.464	.00	.159	.000	**.19**
CAPE Positive	.212	.000	.05	-.057	.045	.00	.046	.106	.00	.067	.019	.00	.092	.001	.01	.069	.000	.07
Suspiciousness	.298	.000	.10	-.174	.000	.03	.032	.239	.00	.076	.005	.01	.045	.100	.00	.137	.000	**.16**
Ideas of Reference	.176	.000	.03	-.039	.173	.00	.046	.107	.00	.069	.016	.01	.043	.130	.00	.046	.000	.05
Affective Dysregulation																		
Depression	.411	.000	**.21**	-.150	.000	.03	.012	.644	.00	.036	.176	.00	.034	.188	.00	.204	.000	**.26**
Anxiety	.331	.000	.12	-.107	.000	.01	-.027	.332	.00	.020	.463	.00	.059	.031	.00	.129	.000	**.15**
Positive Mental Health																		
Well-being	-.401	.000	**.19**	.134	.000	.02	-.016	.546	.00	.000	.999	.00	.053	.046	.01	.187	.000	**.23**
Resilience	-.260	.000	.07	.144	.000	.02	-.065	.019	.00	-.026	.357	.00	.110	.000	.01	.114	.000	.13
Self-esteem	-.341	.000	.12	.152	.000	.03	.001	.963	.00	-.011	.674	.00	.041	.130	.00	.146	.000	**.17**

Factor scores were entered simultaneously to examine their unique contribution. f^2 was calculated separately for each model. Bootstrap procedures (with 2,000 samples) were employed; According to Cohen (1992), f^2 values of .02 or higher indicate small effect sizes, .15 indicate medium effect sizes (highlighted in bold), and ≥ .35 indicate large effect sizes (highlighted in bold and itali

Figure 1. Early Exposome bifactor model.



Note that only the top six items with the highest loadings in the specific factors are presented.

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Chapter 2

Integrating LEGIT and MICE: A Workflow for Robust Gene–Environment Interaction Modelling with Missing Data

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To be submitted

1. Abstract

Standard approaches to gene–environment (G×E) analysis have focused primarily on detecting the presence of an interaction effect, leaving the theoretical form of that interaction, largely unexamined. The competitive-confirmatory framework [Widaman et al., 2012; Belsky et al., 2013] advanced the field by enabling formal statistical comparison among competing G×E models (i.e., diathesis-stress, vantage-sensitivity and differential susceptibility). The **LEGIT R** package [Jolicoeur-Martineau et al., 2020] operationalizes this framework by constructing G×E models with latent genetic and environmental indices and selecting the best-fitting theoretical model through AIC-based competitive-confirmatory comparison.

Detecting G×E interactions demands substantially larger samples than detecting main effects of equivalent magnitude. Missing data, especially endemic to longitudinal and epidemiological research, compound the challenge further. The most common method, listwise deletion, removes any cases with missing values across variables reducing statistical power and, when the probability of missingness is related to variables of interest, introduces bias that distorts true associations. Multiple imputation (MI) is both more efficient and less biased than listwise deletion especially when data are missing at random (MAR), the most plausibly case in complex cohort studies. The **mice** package [van Buuren & Groothuis-Oudshoorn, 2011] implements Multiple Imputation by Chained Equations, generating *m* completed datasets and pooling the resulting estimates via Rubin's rules [Rubin, 1987] to yield a single valid inference. Despite their complementary strengths, integrating the two packages is not straightforward as **LEGIT**'s output objects are incompatible with **mice**'s standard pooling functions.

We present **LEGIT-MI**, a modular R pipeline that bridges this gap through three integrated components: custom pooling of LEGIT fixed-effect estimates via Rubin's rules, aggregation of AIC values across imputations for competitive-confirmatory model selection, and crossover-point estimation for differential susceptibility models. A simulation study confirmed that LEGIT-MI consistently recovers higher statistical power and larger F-ratios than listwise deletion across varying sample sizes and missingness conditions. All code is available at https://github.com/valeriavlgc/LEGIT-MI.

2. Introduction

2.1. Theoretical Frameworks for G×E Research

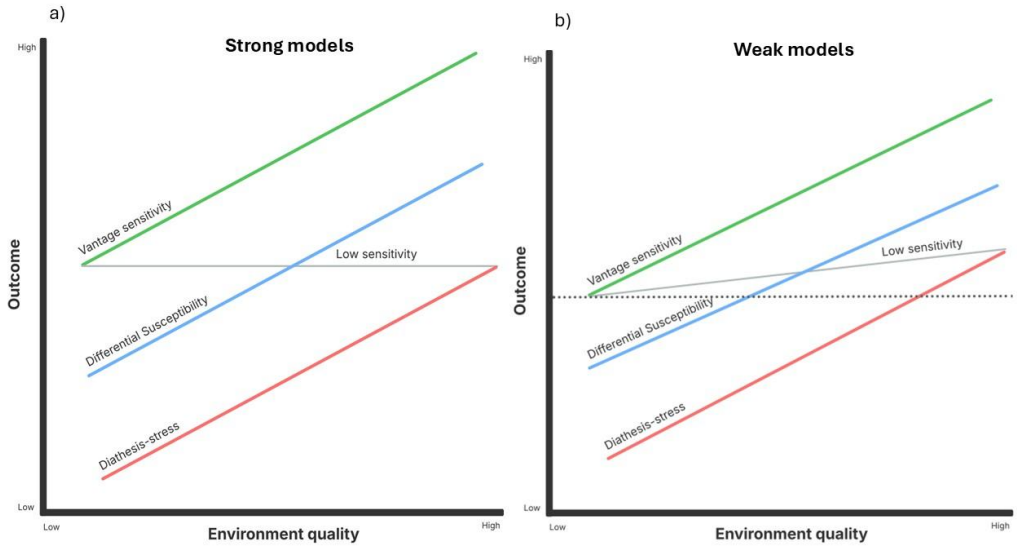
Gene–environment interaction (G×E) research investigates how genetic predispositions and environmental factors jointly influence phenotypic variation, that is observable differences in traits (e.g., behaviour, development, or health outcomes), across individuals. Three major theoretical frameworks have been proposed to explain the mechanistic pathways through which genetic variants moderate environmental effects.

The earliest and most extended is the **diathesis–stress model** [Monroe & Simons, 1991], which posits that genetic risk factors (e.g., "risk alleles") increase vulnerability to adverse environments, but confer no particular advantage in supportive contexts. This model is

represented by the red line in Figure 1. In contrast, the **vantage sensitivity model** [Pluess & Belsky, 2015] proposes that some genetic variants enhance responsiveness exclusively to positive environmental exposures, with minimal or no impact under adverse conditions (green line in Figure 1). Expanding on both, the **differential susceptibility (DS) framework** [Belsky et al., 2007; Belsky & Pluess, 2009; Ellis et al., 2011] proposes that certain genetic variants may index a broader heightened susceptibility to the full spectrum of environmental factors—that is, the same variants involved in amplifying the negative effects of adversity may also increase the potential to benefit from supportive environments (blue line in Figure 1).

All models admit weak and strong versions [Jolicoeur-Martineau et al., 2020]. In strong versions (Figure 1a), only certain individuals are affected by the environmental exposure, meaning they show a clear effect (represented by the diathesis, vantage, and DS models), while others show no response at all (grey line, low-sensitivity individuals). In contrast, the weak versions assume that all individuals are affected by the environment to some degree, but that the magnitude of this effect varies, with some individuals being more affected than others. As shown in Figure 1b, even low-sensitivity individuals exhibit an effect, although it is more attenuated.

Figure 1. Weak and strong versions of the G×E interaction models.



Adapted with permission from Jolicoeur-Martineau et al., 2020.

2.2. Statistical Challenges in Identifying the Form of G×E

2.2.1. Exploratory approaches and their limitations

Early approaches to modelling G×E interactions relied on exploratory methods—primarily hierarchical regression and ANOVA—to test for the presence of an interaction effect, followed by post-hoc probing to characterise its form. The most common probing strategy involved plotting and comparing simple slopes at ±1 SD of the environmental variable [Kochanska et al., 2011; Aiken & West, 1991]. While visually intuitive, this approach carries a fundamental limitation: by anchoring the inspection to two arbitrarily chosen points on the environmental distribution, it may fail to detect effects that emerge only at more extreme values, and it provides

no principled basis for determining the full range of environmental conditions over which the genetic moderator is influential.

The emergence of the DS model called for more discriminating statistical approaches. Developmental methodologists (e.g., [Dearing & Hamilton, 2006]) advocated for the use of *regions of significance* (RoS) analysis, a post-hoc probing technique derived from the Johnson–Neyman technique [Johnson & Neyman, 1936]. In contrast to probing at fixed values, RoS systematically examines the entire continuum of the moderator to identify the exact range(s) of values where the predictor–outcome relationship is statistically significant. [Kochanska et al., 2011] pioneered the application of RoS in G×E research, applying it to the environmental predictor (rather than to the moderator, as is conventional) to determine whether genetic effects were significant only at low environmental values (diathesis–stress), only at high values (vantage sensitivity), or at both extremes (differential susceptibility).

While intuitive and visually informative, RoS analysis has notable limitations [Roisman et al., 2012; Jolicoeur-Martineau et al., 2020]:

> **Sample-size dependence.** Because statistical significance is a function of N, large samples may detect significantly different slopes at both environmental extremes, potentially overestimating support for differential susceptibility.
>
> **Inflated Type I error.** Testing multiple gene–environment pairs without correction compounds false positives. With 10 genetic variants and 5 environmental measures, 50 pairwise tests at $\alpha = .05$ yield a ≈92 % chance of at least one spurious positive.
>
> **Indistinguishability of forms.** RoS cannot formally distinguish between competing sensitivity frameworks when regression slopes do not cross within the observed environmental range, which is critical as slopes predicted under a diathesis–stress model can be visually identical to those under DS.

2.2.2. The competitive-confirmatory approach

To address these shortcomings, [Widaman et al., 2012] and [Belsky, Pluess, & Widaman, 2013] developed a competitive-confirmatory approach that enables direct, formal comparison of alternative theoretical G×E forms. Rather than probing a significant interaction post hoc, this approach reparametrizes the standard regression model so that the crossover point—the value on the environmental continuum at which the high- and low-sensitivity regression lines intersect—becomes a free parameter to be estimated directly, along with its confidence interval. The crossover point is formally defined as $\hat{c} = -\beta^{G}/\beta^{LG}$, and its location relative to the observed environmental range is the key criterion for distinguishing between theoretical frameworks: a crossover falling near the lower end of the environmental distribution is consistent with vantage sensitivity, one falling within the observed range supports differential susceptibility, and one falling at or beyond the upper end indicates diathesis–stress.

This methodology was further refined into a two-stage framework [Belsky et al., 2018]. In the first, exploratory stage, a standard regression model is fitted to assess the magnitude of the interaction effect—not to require a significant p-value as a prerequisite, but to evaluate the F-ratio and obtain starting values for the nonlinear estimation. In the second, confirmatory stage, the six theoretical models are fitted and compared as described above. This combined approach

preserves the statistical power advantages of confirmatory testing while using the exploratory phase as a practical diagnostic step.

2.3. The LEGIT Package

The **LEGIT** R package (Latent Environmental and Genetic InTeraction; [Jolicoeur-Martineau et al., 2020]) operationalizes the two-stage competitive-confirmatory framework described above. The package provides two primary functions corresponding to the two analytical stages.

The first function, `LEGIT()`, handles the exploratory stage, fitting a standard G×E regression model that estimates the main effects of the latent genetic and environmental variables and their interaction. It produces two key outputs that serve as a filter for proceeding to the confirmatory stage: the F-ratio for the interaction term, which indicates whether there is sufficient evidence of an interaction, and the regression coefficients, which serve as starting values for the subsequent nonlinear estimation:

```
LEGIT(data, genes, env, formula = y ~ G*E + covariates)
```

The second function, `GxE_interaction_test()`, implements the confirmatory stage. It fits and compares the six theoretical nested models using AIC or BIC:

```
GxE_interaction_test(data = data,  genes = genes,  env =
env,
                     formula_noGxE = Y ~ 1,
                     crossover = c("min", "max"),
                     criterion = "AIC",
                     lme4 = FALSE,  rescale = TRUE)
```

The six nested models are fitted (the weak and strong versions of each of the three GxE models) and their fit is evaluated using the Akaike information criterion (AIC) or the Bayesian information criterion (BIC), with the best-fitting model identified by the lowest value. In the strong version of each model, the slope of the less sensitive group is fixed at zero, reflecting the assumption that this group is entirely unaffected by the environment; in the weak version, this slope is freely estimated, allowing for a smaller but non-zero environmental effect. To guard against false positives, four additional models without a G×E interaction term are also fitted (intercept only, gene only, environment only, and gene + environment only): if any of these yields the lowest AIC or BIC, the data are classified as showing no evidence of G×E.

Both functions additionally support mixed-effects modelling via the **lme4** package [Bates et al., 2015], making them suitable for clustered or longitudinal data structures. Simulation studies have demonstrated that the competitive-confirmatory approach implemented in **LEGIT** substantially outperforms RoS, particularly in small samples and for moderate effect sizes, achieving near-perfect classification accuracy at $N \geq 500$ with a medium effect size ($R^2 \geq .20$; [Jolicoeur-Martineau et al., 2020]).

2.4. The Missing Data Problem

A persistent challenge in G×E research is incomplete data across genetic, environmental, and phenotypic variables [Newman, 2003; Herrera-Luis et al., 2024]. This is particularly consequential for three reasons. First, detecting interaction effects already requires substantially larger samples than detecting main effects alone, typically 4 times the sample size, so any additional case-loss due to missing data further erodes already limited statistical power [Thomas, 2010]. Second, **listwise deletion**, the most common default approach, excludes any case with a missing value on any variable in the model; this not only directly reduces the available sample size, but more critically, when missingness is not random (e.g., higher-risk participants being more likely to drop out), the analyzed sample is no longer representative of the original population, yielding biased parameter estimates [Newman, 2003; Heymans & Twisk, 2022].

Third, missingness patterns often differ systematically across data types: genetic data may be missing due to failed assays, environmental data due to participant non-response, and phenotypic data due to longitudinal attrition, creating a complex, multivariate missingness structure that standard approaches are not well suited to address [Lee et al., 2023].

Single imputation methods, such as mean substitution or regression imputation, address attrition by generating one complete dataset. However, because imputed values are treated as if they were observed, these approaches systematically underestimate variance and inflate Type I error rates, producing standard errors and confidence intervals that are too narrow [Little & Rubin, 1987].

Multiple imputation (MI) provides a principled solution to these problems. Rather than filling in each missing value once, MI generates *m* complete datasets, each with missing values replaced by independent draws from the appropriate conditional distribution—that is, plausible values given all observed information. Each of the *m* datasets is then analysed separately using the intended statistical model, and the results are combined using Rubin's rules [Rubin, 1987]. The pooled point estimate ($\bar{Q}$) is the average of the *m* estimates, and the total variance has two components: the average within-imputation variance ($\bar{U}$), which reflects ordinary sampling uncertainty, and the between-imputation variance (B), which captures the additional uncertainty attributable to the fact that the missing values are not known exactly: $\bar{Q} = (1/m)\Sigma_j \hat{Q}^{+j)}$, with total variance $T = \bar{U} + (1 + m^{-1})B$. By explicitly separating and combining these two sources of uncertainty, MI yields valid standard errors and hypothesis tests that properly reflect the incomplete nature of the data, unlike both listwise deletion and single imputation [Schafer & Graham, 2002].

2.5. The mice Package

The **mice** package [van Buuren & Groothuis-Oudshoorn, 2011] implements Multiple Imputation by Chained Equations (MICE), the dominant method for generating multiply imputed datasets in R. Rather than imputing all missing values at once, **mice** handles each incomplete variable in turn, specifying a separate predictive model for each variable with missing values using all other variables in the dataset as predictors. Crucially, the imputation method is tailored to the type of each variable: predictive mean matching (PMM) [Little, 1988]

for continuous variables, logistic regression for binary variables, and polytomous regression for unordered categorical variables. Each method fills in missing values by drawing plausible values given the observed data, thereby preserving the distributional properties of each variable and avoiding implausible imputed values. The algorithm cycles through all incomplete variables repeatedly until the imputed values stabilize.

Other imputation approaches exist in R, including **mi** [Su et al., 2011]; **Amelia**, optimised for time-series data [Honaker et al., 2011]; and **missForest**, which uses random forests [Stekhoven & Bühlmann, 2012]. However, **mice** remains the most widely used due to its interpretability, computational efficiency, and versatility in handling mixed data types [Azur et al., 2011; van Buuren, 2018].

2.5.1 The Standard mice Workflow

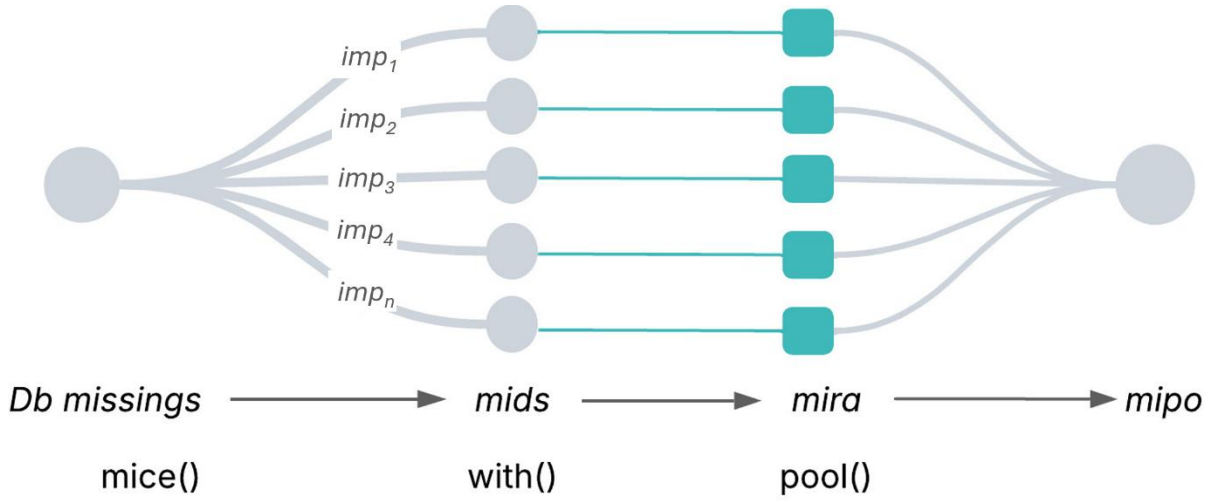
The standard **mice** workflow follows three steps (Figure 2):

Imputation via `mice()`: takes the incomplete dataset and generates *m* imputed datasets, each with missing values replaced by plausible draws from the appropriate conditional distribution, storing them together in a single object of class `mids` (multiply imputed datasets).

Analysis via `with()`: fits the intended statistical model to each of the *m* completed datasets separately, producing *m* sets of parameter estimates that differ slightly across datasets because each imputation introduced different plausible values for the missing observations; this variation is precisely what captures the uncertainty due to missingness. The results are stored in an object of class `mira` (multiply imputed repeated analyses).

Pooling via `pool()`: takes the `mira` object and combines the *m* sets of estimates into a single set of pooled estimates, standard errors, and p-values using Rubin's rules, properly accounting for both the within-imputation variance (ordinary sampling uncertainty) and the between-imputation variance (uncertainty due to the missing data itself).

Figure 2. Main steps of the multiple imputation process using mice.



2.6 The Present Workflow

Although **LEGIT** and **mice** are both well-established tools for their respective purposes, no existing workflow integrates them for competitive-confirmatory G×E analysis with missing data. The incompatibility arises because **LEGIT** returns complex nested objects (`fit_main`, `fit_genes`, `fit_env`) that `mice::pool()` cannot process, and `GxE_interaction_test()` returns list-based model rankings rather than tidy coefficient tables, meaning that neither the analysis step nor the pooling step of the standard **mice** pipeline can be applied directly.

We present LEGIT-MI, an R pipeline that integrates multiple imputation with competitive-confirmatory G×E analysis. The pipeline: (1) simulates G×E data with configurable sample sizes and missingness proportions under both MCAR and MAR mechanisms; (2) imputes missing values using **mice** with a fully informed predictor matrix that includes auxiliary variables and outcome variables as predictors; (3) fits **LEGIT** models across all imputed datasets and pools results using Rubin's rules via a custom pooling workflow, since **LEGIT** objects are not directly compatible with `mice::pool()`; and (4) applies `GxE_interaction_test()` across imputations, pools AIC values, and selects the best-fitting theoretical model (diathesis–stress, vantage sensitivity, or differential susceptibility). By unifying these steps, LEGIT-MI enables reproducible and statistically rigorous G×E analysis in the presence of missing data. The pipeline supports both unilevel and multilevel (**lme4**) model specifications and is available at https://github.com/valeriavlgc/LEGIT-MI.

3. Simulation Study

To evaluate the proposed methods under controlled conditions, we generated synthetic data mimicking a realistic G×E study design with correlated predictors, structured outcome models, and moderate effect sizes. The simulation framework was implemented in R using the **MASS** package to generate correlated continuous variables by sampling from multivariate normal distributions.

3.1 Data Generation

We simulated a sample of size *n* from a multivariate generative model comprising two continuous genetic indicators (G1, G2), two environmental exposures (E1, E2), two model covariates (C1, C2), two outcomes (Y1, Y2), and six auxiliary variables (Aux1–Aux6). The auxiliary variables are included solely to support the imputation model and are not part of the LEGIT analysis (Section 3.2).

Genetic indicators were drawn from a bivariate standard normal distribution with mild correlation (r = 0.3):

```
cor_genes   <- matrix(c(1, 0.3, 0.3, 1), nrow = 2)
Sigma_genes <- diag(2) %*% cor_genes %*% diag(2)
genes <- mvrnorm(n, mu = c(0, 0), Sigma = Sigma_genes)
colnames(genes) <- c("G1", "G2")
```

Environmental indicators were drawn with moderate inter-correlation (r = 0.4) and unit standard deviations:

```
cor_envs   <- matrix(c(1, 0.4, 0.4, 1), nrow = 2)
Sigma_envs <- diag(2) %*% cor_envs %*% diag(2)
envs <- mvrnorm(n, mu = c(0, 0), Sigma = Sigma_envs)
colnames(envs) <- c("E1", "E2")
```

Model covariates were generated independently from standard normal distributions:

```
C1 <- rnorm(n, mean = 0, sd = 1)
C2 <- rnorm(n, mean = 0, sd = 1)
```

Six continuous auxiliary variables (Aux1–Aux6) were generated with the following correlation structure to reflect the auxiliary information typically available in real epidemiological studies: Aux3 is correlated with E1 ($r \approx 0.80$); Aux4 is correlated with G1 ($r \approx 0.85$); Aux5 is correlated with G2 ($r \approx 0.80$), directly aiding imputation of the second genetic indicator; and Aux6 is correlated with E2 ($r \approx 0.80$), directly aiding imputation of the second environmental indicator. Aux1 and Aux2 are additional continuous measures with weaker associations. Because all six variables correlate with the analysis variables, including them in the imputation model improves the quality of imputed values for G1, G2, E1, and E2 without distorting the G×E structure. All auxiliary variables remain fully observed throughout the simulation.

3.2 Outcome Models

The latent genetic and environmental indices are constructed as weighted linear combinations of the mean-centred indicators. The true weights used to generate the data are $w^G = (0.6, 0.4)$ for the genetic index and $w^e = (0.7, 0.3)$ for the environmental index:

```
G_latent <- 0.6 * scale(G1, center=TRUE, scale=FALSE) +
            0.4 * scale(G2, center=TRUE, scale=FALSE)
E_latent <- 0.7 * scale(E1, center=TRUE, scale=FALSE) +
            0.3 * scale(E2, center=TRUE, scale=FALSE)
```

Two outcomes were constructed as linear functions of the latent indices, their interaction, covariates, and auxiliary effects:

Y1 (positive environment): $lp_1 = \beta_0 + \beta^G G_{latent} + \beta^e E_{latent} + \beta^{LG} (G_{latent} \times E_{latent}) + \beta C_1 C1 + \beta C_2 C2 +$ auxiliary effects

Y2 (adverse environment): $lp_2 = \beta_0 + \beta^G G_{latent} - \beta^e E_{latent} + \beta^{LG} (G_{latent} \times (-E_{latent})) + \beta C_1 C1 + \beta C_2 C2 +$ auxiliary effects

Fixed coefficients were $\beta_0 = 0$, $\beta^G = 0.3$, $\beta^e = 0.3$, $\beta^{LG} = 0.5$, $\beta C_1 = 0.1$, $\beta C_2 = -0.1$. The G×E coefficient $\beta^{LG} = 0.5$ corresponds to a medium-large interaction effect ($R^2 \approx 15$–20 % for the G×E term alone). Outcomes were generated by adding independent Gaussian residuals with SD = 1. Y2 uses the negated environmental variable to model a scenario in which higher scores on E2 correspond to greater adversity rather than greater support. Because the direction of the environmental effect is reversed, the theoretical model classification must also be reversed: a pattern identified as diathesis-stress under a positive environment corresponds to vantage sensitivity under an adverse one. The pipeline handles this automatically via the `neg_env`

argument and the `revert_model()` utility function, allowing verification that model classification is correct across both positive and adverse environmental contexts.

3.3 Missing Data Mechanisms

To evaluate the pipeline under two qualitatively different patterns of missingness, missing values were introduced separately under Missing Completely At Random (MCAR) and Missing At Random (MAR) mechanisms. In both cases, only the eight analysis variables (G1, G2, E1, E2, C1, C2, Y1, Y2) received missing values; the six auxiliary variables (Aux1–Aux6) remained fully observed throughout.

MCAR. Under MCAR, missing values were introduced at two levels, 15% and 25%, to evaluate pipeline performance across a moderate and a more demanding missingness scenario. In both cases, entries were randomly deleted independently for each analysis variable with equal probability across all observations.

```
n_miss <- round(nrow(dt) * 0.15)
for (var in analysis_vars) {
  miss_idx          <- sample(nrow(dt), n_miss)
  dt[miss_idx, var] <- NA
}
```

Cell-level (rather than row-level) deletion was used to ensure that missingness in one variable is independent of missingness in any other, preserving the information that **mice** exploits when imputing each variable from the others. Under MCAR, listwise deletion is unbiased: the complete cases remaining after deletion are a random subsample of the original data, so parameter estimates are not distorted. However, listwise deletion still discards all cases with any missing value, which directly reduces the effective sample size and therefore statistical power. The main advantage of MI under MCAR is thus efficiency rather than bias correction.

MAR. Under MAR, the probability of a value being missing depends on other observed variables (here, the auxiliary variables), but not on the missing value itself. This creates a realistic pattern in which MI, having access to the auxiliary predictors of missingness, can recover valid estimates, whereas listwise deletion becomes biased. Missingness for each analysis variable is driven by a dedicated auxiliary predictor: Aux4 ($r \approx 0.85$ with G1) drives G1 missingness, Aux5 ($r \approx 0.80$ with G2) drives G2 missingness, Aux3 ($r \approx 0.80$ with E1) drives E1 missingness, and Aux6 ($r \approx 0.80$ with E2) drives E2 missingness. Missingness in C1, C2, Y1, and Y2 is driven by Aux1. Missing entries are selected by weighted sampling, so that observations with higher auxiliary values are more likely to be assigned missing:

```
mar_predictor <- function(var) {
  if      (var == "G1")  dt[["Aux4"]]
  else if (var == "G2")  dt[["Aux5"]]
  else if (var == "E1")  dt[["Aux3"]]
  else if (var == "E2")  dt[["Aux6"]]
  else                   dt[["Aux1"]]
}
```

```
weights  <- pred - min(pred) + 1e-6
miss_idx <- sample(nrow(dt), n_miss, prob = weights, replace = FALSE)
```

Because the variables that drive missingness (Aux1–Aux6) are always observed and are included in the imputation model (Section 3.2), **mice** can exploit them to recover the missing information—this is precisely the scenario in which MI is expected to offer the greatest advantage over listwise deletion.

4. Multiple Imputation with mice

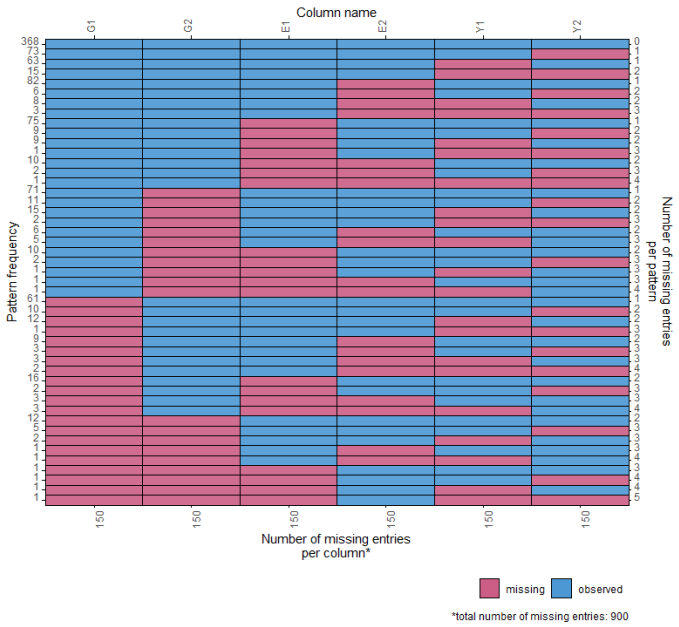
To address the simulated missing data, we implemented a multiple imputation workflow encapsulated in an `imputate_data()` function. The procedure comprises three stages: pre-imputation diagnostics, imputation model specification, and quality checking of the imputed values.

4.1 Pre-Imputation Diagnostics

Before running imputations, we examined the extent, structure, and mechanism of missingness. The `ggmice::plot_pattern()` function produces a visual summary of missingness patterns across all variables. Figure 3 shows an example of the missingness pattern under MCAR: missing values are uniformly distributed with no particular combination of variables dominating, confirming the absence of systematic dropout.

```
plot_pattern(dt_miss, vrb = c("G1","G2","E1","E2","Y1","Y2"),
             square = FALSE, rotate = TRUE)
```

Figure 3. Missing data patterns under MCAR at 15% missingness per variable.



Note. Each row represents a missingness pattern across the eight analysis variables (G1, G2, E1, E2, C1, C2, Y1, Y2). Auxiliary variables (Aux1–Aux6) are fully observed and not shown.

To formally evaluate the MCAR assumption, we applied Little's test [Little, 1988] using `naniar::mcar_test()`. A non-significant result ($p > .05$) supports MCAR. A significant result would not preclude imputation under MAR, since **mice** handles both mechanisms consistently provided the variables that predict missingness are included in the imputation model, but would prompt additional covariate adjustment.

```
mcar <- mcar_test(dt_miss)
if (mcar$p.value > 0.05) {
  message("Data is likely MCAR (p = ", round(mcar$p.value, 4),
").")
} else {
  message("Proceeding under MAR assumption.")
}
```

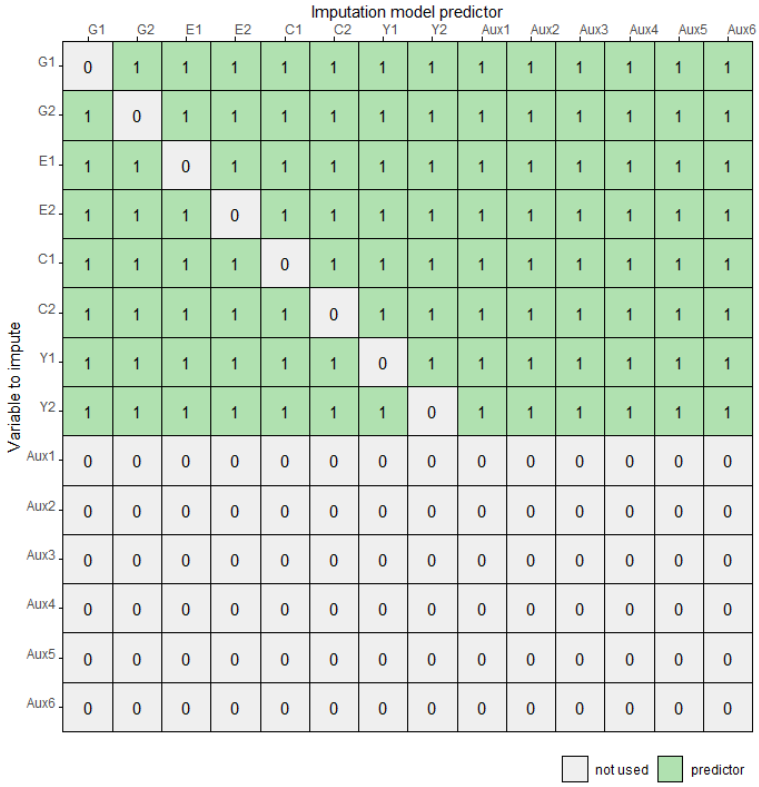
4.2 Imputation Model Specification

We used a fully-informed predictor matrix: by default, `make.predictorMatrix()` creates a matrix in which every observed variable is used as a predictor for every incomplete variable, maximizing the information available to the imputation model at each step. We then set the rows corresponding to the auxiliary variables (Aux1–Aux6) to zero, indicating that the auxiliary variables are never imputed (they are always fully observed) but remain as predictors (columns) for all analysis variables:

```
predictor_matrix <- make.predictorMatrix(dt_miss)
aux_vars <- c("Aux1", "Aux2", "Aux3", "Aux4", "Aux5", "Aux6")
predictor_matrix[aux_vars, ] <- 0
```

This fully-informed specification means that each analysis variable is imputed from all other analysis variables *and* from all six auxiliary variables simultaneously. This is the recommended approach when auxiliary variables are available [Collins et al., 2001; van Buuren, 2018]: including them in the imputation model allows **mice** to exploit their correlations with the analysis variables to improve imputation quality. Crucially, Aux4 ($r \approx 0.85$ with G1) and Aux5 ($r \approx 0.80$ with G2) directly improve the imputation of the genetic indicators, while Aux3 ($r \approx 0.80$ with E1) and Aux6 ($r \approx 0.80$ with E2) improve the imputation of the environmental indicators. The `ggmice::plot_pred()` function renders the predictor matrix graphically (Figure 4).

Figure 4. Predictor matrix used in the MICE imputation model.



Note. Each cell indicates whether the column variable (predictor) is used to impute the row variable (target). Green cells indicate active predictors (value = 1); grey cells indicate excluded predictors (value = 0). The diagonal is always 0 since a variable cannot predict itself. Rows corresponding to auxiliary variables (Aux1–Aux6) are set to 0 throughout, as these variables are fully observed and serve exclusively as predictors, never as imputation targets.

4.3 Imputation Procedure and Diagnostics

We generated $m = 10$ imputed datasets using predictive mean matching (PMM), an appropriate method for continuous variables that preserves the marginal distribution by replacing missing values with observed values closest in predicted value:

```
data_imp <- mice(dt_miss, m = nimp, maxit = 5,
                 method          = "pmm",
                 predictorMatrix = predictor_matrix,
                 seed            = seed,
                 printFlag       = verbose)
```

We assessed imputation quality through four complementary diagnostics: (1) *Density overlay plots*: overlaid histograms of observed and imputed values confirm distributional alignment. (2) *Scatter plots*: `xyplot(data_imp, Y2 ~ E2)` checks whether the bivariate relationship between Y2 and E2 is preserved across imputations—a key check for maintaining interaction effects. (3) *Stripplot*: `stripplot(data_imp)` displays imputed values stratified by imputation number. (4) *Jitter plot*: `ggmice(data_imp, aes(x = .imp, y = Y1)) + geom_jitter()` provides a per-variable view of imputed value spread across the m datasets.

5. LEGIT Analysis with Multiple Imputation

With $m = 10$ imputed datasets, we apply the two-stage **LEGIT** workflow to each completed dataset and pool results. Because **LEGIT** returns custom S3 objects (complex nested output objects) incompatible with `mice::pool()`, we implemented a custom pooling strategy operating directly on extracted coefficient tables.

5.1 Stage 1: Exploratory Latent G×E Modelling

For each imputed dataset j = 1,…,m, we extract the completed data and fit a **LEGIT** model:

```
for (j in 1:nimp) {
  data_complete <- complete(dt_imp, action = j)
  env   <- data_complete[, params$env,   drop = FALSE]
  genes <- data_complete[, params$genes, drop = FALSE]
  fit   <- LEGIT(data    = data_complete,
                 genes   = genes,
                 env     = env,
                 formula = Y1 ~ G*E + C1 + C2,
                 lme4    = FALSE,
                 rescale = FALSE)
  fits[[j]] <- fit
}
```

For multilevel designs (e.g., twin or longitudinal data), the formula is extended with a random-intercept term and `lme4 = TRUE`: `formula = Y1 ~ G*E + C1 + C2 + (1|subject_id)`. This produces m separate **LEGIT** fits, each yielding estimates of the genetic score weights $\hat{p}$, environmental score weights $\hat{q}$, and main-model coefficients (β_0, β^E, β^G, β^{LG}).

5.2 Custom Pooling of Fixed-Effect Estimates

Because `pool()` requires a `mira` object, we extract coefficient tables manually and apply Rubin's rules via `mice::pool.table()` (available since **mice** 3.17.6):

```
for (x in 1:nimp) {
  fe <- summary(fits[[x]]$fit_main)$coefficients
  fit_df_list[[x]] <- data.frame(
    term        = rownames(fe),
    estimate    = fe[, "Estimate"],
    std.error   = fe[, "Std. Error"],
    residual.df = rep(NA, nrow(fe)))
}
w <- do.call(rbind, fit_df_list)
pooled_fits <- pool.table(w,
```

```
                          type = "all", conf.int = TRUE, conf.level =
0.95,
                          dfcom = nrow(data_complete) -
length(coef(fits[[1]]$fit_main)),
                          rule = "rubin1987")
```

Pooled Wald chi-squared statistics and p-values for each term are then computed as:

```
anova_results <- pooled_fits |>
  mutate(chisq   = (estimate / std.error)^2,
         p.value = pchisq(chisq, df = 1, lower.tail = FALSE)) |>
  select(term, estimate, std.error, chisq, p.value)
```

This yields valid inference for the G×E interaction term (`G:E`) and all covariates, properly accounting for both within- and between-imputation variability.

5.3 Visualization

Interaction plots are generated from a representative imputed dataset (typically j = 1) using **LEGIT**'s built-in `plot()` method:

```
plot(fits[[1]], ylab = "Outcome", xlab = "Environmental Score",
cex.leg = 1.2)
```

The plot displays predicted outcome trajectories as a function of the environmental score, stratified across quantiles of the genetic score (default: 2.5th, 50th, 97.5th percentiles), with covariates fixed at their means. To assess stability across imputations, we recommend inspecting plots from multiple imputations side-by-side; systematic differences in the pattern of lines across imputations would signal sensitivity to the imputation model.

5.4 Stage 2: Competitive-Confirmatory Model Comparison via AIC Pooling

We apply `GxE_interaction_test()` to each imputed dataset to obtain AIC values for all six sensitivity models plus the four non-interaction comparison models:

```
GxE_results <- lapply(1:nimp, function(k) {
  imp_data <- complete(dt_imp, k)
  genes    <- imp_data[, params$genes, drop = FALSE]
  env      <- imp_data[, params$env,   drop = FALSE]
  suppressWarnings(
    GxE_interaction_test(data = imp_data, genes = genes, env = env,
                         formula_noGxE = Y1 ~ 1,
                         crossover = c("min", "max"),
                         criterion = "AIC",
                         lme4 = FALSE, rescale = TRUE))
})
```

AIC values are extracted for all ten models across all m imputations and stored in a 10×m matrix. Pooled AIC values are obtained by averaging: $\overline{AIC}_k = (1/m)\Sigma_j AIC_k^{+j)}$. The model with the lowest $\overline{AIC}$ is selected. When the difference between the first and second ranked models falls within a tolerance threshold ($\delta\overline{AIC} < 1$), a tie is declared and both models are reported:

```
pooled_aic <- rowMeans(aic_matrix, na.rm = TRUE)
sorted_aic <- sort(pooled_aic)
best_model <- names(sorted_aic)[1]
tie_model  <- abs(sorted_aic[1] - sorted_aic[2]) <= tolerance
```

Note on AIC pooling. AIC averaging across imputations is a pragmatic approximation. It is not equivalent to computing AIC from a pooled likelihood, which is not straightforward for alternating-optimisation models. For the purpose of comparative model selection, averaged AIC provides a consistent and interpretable decision rule. Sensitivity analyses comparing BIC-pooled selections are straightforward to implement by passing `criterion = "BIC"` to `GxE_interaction_test()`.

5.5 Crossover-Point Estimation

When the best-fitting model is differential susceptibility (weak or strong), we average crossover-point estimates across imputations. **LEGIT** stores crossover values as character strings of the form "(lower / upper)" encoding the 95 % confidence interval. A utility function (`calculate_crossover()`) parses these strings, extracts the bounds, and computes the mean across imputations. The averaged crossover interval is reported alongside the AIC-selected model. Per [Jolicoeur-Martineau et al., 2020], a DS classification is upheld only when the averaged crossover 95 % confidence interval falls within the observed range of the environmental score; otherwise the model is reclassified as the next-best alternative.

6. Analysis Pipeline: The run_analysis_LEGIT() Function

To automate the application of the above steps across all combinations of genetic variables, environmental exposures, and outcomes, we developed `run_analysis_LEGIT()`. This modular function supports both standard (complete-case) and MI workflows, and handles both unilevel and multilevel specifications:

```
run_analysis_LEGIT <- function(genes_values, env_values, out_values,
dt,
                               analysis_type, imputated,
                               multilevel_id = NULL,
                               save_results  = TRUE,
                               verbose       = TRUE)
```

Each result row contains: the combination identifier; pooled p-values for G, E, covariates, and the G×E term; the pooled Wald chi-squared statistic; the best-fitting interaction model; its

pooled AIC; any crossover interval; whether a tie was detected; and the second-best model with its AIC. Results are written to timestamped `.xlsx` files.

The full pipeline is executed from a single entry-point script that runs complete-data, MCAR listwise, MCAR imputed, MAR listwise, and MAR imputed analyses for each gene–environment–outcome combination:

```
source("config.R"); source("utils.R")
source("data_simulation.R"); source("data_imputation.R");
source("data_analysis_LEGIT.R")


dt           <- simulate_data(n = 500, seed = 123)
dt_miss_mcar <- missings_data_MCAR(dt, percentage = 0.20, seed = 123)
dt_miss_mar  <- missings_data_MAR( dt, percentage = 0.20, seed = 123)
dt_imp_mcar  <- imputate_data(dt_miss_mcar, seed = 123, verbose =
FALSE)
dt_imp_mar   <- imputate_data(dt_miss_mar,  seed = 123, verbose =
FALSE)


genes_values <- c("G1", "G2");  env_values <- c("E1", "E2")
out_values   <- c("Y1");  analysis_type <- ANALYSIS_TYPE$UNILEVEL


# Five conditions: complete, MCAR listwise, MCAR MICE, MAR listwise,
MAR MICE
run_analysis_LEGIT(genes_values, env_values, out_values,
                   dt,           analysis_type, imputated = FALSE)
run_analysis_LEGIT(genes_values, env_values, out_values,
                   dt_miss_mcar, analysis_type, imputated = FALSE)
run_analysis_LEGIT(genes_values, env_values, out_values,
                   dt_imp_mcar,  analysis_type, imputated = TRUE)
run_analysis_LEGIT(genes_values, env_values, out_values,
                   dt_miss_mar,  analysis_type, imputated = FALSE)
run_analysis_LEGIT(genes_values, env_values, out_values,
                   dt_imp_mar,   analysis_type, imputated = TRUE)
```

Scalability. The pipeline scales naturally to multiple genetic variables, environmental exposures, and outcomes. For each combination of genetic variable, environmental exposure, and outcome, a separate LEGIT model is fitted across all m imputed datasets. Results for all combinations are written to a single timestamped `.xlsx` file, allowing straightforward comparison and reproducibility.

7. Results

Table 1 presents power, mean F-ratio, and bias of the GxE interaction estimate across all simulation conditions. Complete-data power was 100% across all conditions and sample sizes,

confirming that the true interaction (b\textsubscript{GxE} = ±0.50) was consistently detectable in the absence of missing data.

Under MCAR, MI maintained substantially higher power and mean F-ratio than listwise deletion across all conditions. At n = 250 with 20% missingness, listwise power dropped to 66–72% while MI retained 84–96%. The F-ratio advantage was consistent and grew with missingness percentage, at n = 1000 with 20% missing, MI recovered mean F-ratios of 47–48 compared to 25–26 for listwise, representing a roughly 90% increase in recovered signal. Bias for both methods was small and near zero under MCAR, consistent with the theoretical expectation that listwise deletion is unbiased when data are missing completely at random.

Under MAR, MI again outperformed listwise on power and F-ratio across all conditions. The advantage was most pronounced at smaller sample sizes and higher missingness: at n = 250 with 20% missingness, listwise power was 66–72% versus 88–96% for MI. Contrary to theoretical expectation, listwise bias under MAR was small and near zero across all conditions, suggesting that the simulated MAR mechanism, while correctly structured, was not strong enough to produce meaningful bias in complete-case estimates at the sample sizes tested. MI showed consistent small negative bias (approximately −0.09 to −0.17) attributable to attenuation from imputation noise, which is a known and acceptable property of MI when the fraction of missing information is moderate.

Across all conditions, power and F-ratio increased with sample size, and the absolute advantage of MI over listwise was greatest at higher missingness rates, confirming that the efficiency gains from MI are most consequential precisely when missingness is most damaging to statistical power.

8. Discussion

We have presented LEGIT-MI, a complete, modular R workflow that integrates **LEGIT** for latent G×E modelling with **mice** for multiple imputation. The key methodological contributions are: (1) a custom Rubin's-rules pooling procedure for **LEGIT** fixed-effect estimates that bypasses the need for a `mira` object; (2) AIC averaging across imputations as a practical criterion for competitive-confirmatory model selection; and (3) crossover-point averaging for differential susceptibility classification.

Why MI matters for G×E. G×E interactions are among the most statistically demanding effects in the behavioural and developmental sciences. Listwise deletion compounds power deficits by discarding cases that are often systematically different from completers. MI preserves sample size and, crucially, maintains the covariance structure between genetic and environmental variables that underlies the interaction — ensuring that imputed values are consistent with potential G×E effects. The inclusion of auxiliary variables that correlate directly with each analysis variable further improves imputation quality by providing the imputation model with targeted information about missing values, a strategy known as the inclusive

imputation model [Collins et al., 2001]. The simulation results confirm this efficiency advantage: across all conditions, MI recovered substantially higher F-ratios and power than listwise deletion, with gains increasing at higher missingness rates. The bias advantage of MI over listwise under MAR was less pronounced than expected in these simulations, likely reflecting a MAR mechanism of moderate strength; future work should examine stronger MAR conditions to characterize the full bias-correction benefit of MI.

Limitations and future directions. Several limitations should be noted. First, our simulation used MCAR and MAR missingness; under MNAR, sensitivity analyses such as pattern-mixture models would be needed. Second, AIC pooling across imputations is an approximation; a likelihood-ratio-based approach would be preferable if the pooled likelihood could be recovered from **LEGIT**'s iterative optimisation framework. Third, the current implementation uses a single representative imputed dataset for visualisation; pooled interaction plots averaging predicted values across all m fits would provide more principled visual summaries. Fourth, the pipeline does not yet include a data-driven strategy for selecting the number of imputations m; we recommend setting m toward the fraction of missing information [White et al., 2011] when missingness exceeds 20–30%. Finally, extension to genome-wide analyses incorporating large numbers of genetic variants simultaneously would require a variable selection step — such as elastic net weighting within **LEGIT**'s `elastic_net_var_select()`) before the iterative optimization stage [Jolicoeur-Martineau et al., 2020].

9. Conclusion

We have demonstrated a principled, end-to-end workflow for robust gene–environment interaction modelling in the presence of missing data, combining the competitive-confirmatory power of **LEGIT** with the variance-preserving imputation capabilities of **mice**. Simulation results confirm that the MI pipeline consistently recovers higher statistical power and larger F-ratios than listwise deletion across all tested sample sizes and missingness conditions, with the advantage most pronounced at higher missingness rates. The workflow is fully modular — researchers can substitute their own genetic variables, environmental exposures, outcomes, and covariates with minimal code modification, and can switch between unilevel and multilevel specifications via a single configuration flag. We encourage developmental researchers and behavioural geneticists to adopt this integrated approach when faced with the combination of latent G×E modelling and incomplete data that characterises most real longitudinal cohort studies.

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Table 1. Power (%), mean F-ratio, and bias by sample size, missingness percentage, and condition (50 replications per condition).

			Power (%)		Mean F-ratio		Bias		Power (%)		Mean F-ratio		Bias	
			MCAR						MAR					
N	Miss.	Out.	MI	LW	MI	LW	MI	LW	MI	LW	MI	LW	MI	LW
250	15%	Y1	**100%**	88%	**15.9**	12.2	-0.087	0.060	**96%**	82%	**16.0**	11.9	-0.087	0.045
250	15%	Y2	**98%**	88%	**15.8**	11.1	-0.092	0.043	**98%**	82%	**15.9**	10.2	-0.094	0.059
250	20%	Y1	**94%**	66%	**11.6**	7.8	-0.138	0.061	**96%**	72%	**11.7**	7.4	-0.127	0.051
250	20%	Y2	**84%**	72%	**9.9**	7.4	-0.167	0.085	**88%**	66%	**10.9**	8.4	-0.152	0.084
500	15%	Y1	**100%**	94%	**32.2**	21.0	-0.088	-0.016	100%	100%	**30.2**	20.3	-0.098	-0.003
500	15%	Y2	100%	100%	**28.6**	20.7	-0.105	0.027	100%	100%	**29.0**	20.6	-0.100	0.009
500	20%	Y1	**100%**	86%	**20.8**	12.9	-0.152	-0.019	**100%**	86%	**21.7**	12.4	-0.146	-0.033
500	20%	Y2	**100%**	94%	**25.2**	15.1	-0.116	0.033	**100%**	90%	**23.6**	14.0	-0.127	0.003
1000	15%	Y1	100%	100%	**64.1**	43.6	-0.084	0.022	100%	100%	**58.5**	38.0	-0.100	-0.014
1000	15%	Y2	100%	100%	**61.0**	39.0	-0.083	0.007	100%	100%	**59.4**	40.6	-0.089	0.011
1000	20%	Y1	100%	100%	**47.2**	25.3	-0.131	-0.017	100%	100%	**48.8**	27.1	-0.129	0.007
1000	20%	Y2	100%	100%	**48.0**	26.1	-0.119	0.010	**100%**	98%	**48.1**	25.3	-0.122	-0.015

Note. 50 simulation replications per condition. MI = multiple imputation via MICE (m = 10); LW = listwise deletion; Miss. = % of missing values. Out. = outcome variable. True bGxE = ±0.50. Bias = mean $|\hat{b}GxE| - 0.50$. Bold values indicate MI outperforms listwise on the given metric

SECTION 2

TESTING NOVEL G×E INTERACTIONS FROM A DIFFERENTIAL SUSCEPTIBILITY APPROACH

Translational Psychiatry

Chapter 3

Time to Incorporate Positive Experiences and Outcomes in Psychosis Research: Genetic Differential Susceptibility to Childhood Experiences Works for "Better and for Worse"

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Abstract

Research on gene-environment interactions in psychosis has been guided by diathesis-stress models, which emphasize the role of negative experiences. In contrast, the Differential Susceptibility (DS) model indicates that individuals differ in sensitivity to both adverse and supportive environments. This study replicates and expands an initial proof-of-concept DS study on psychosis by examining whether genetic sensitivity to the environment, indexed by polygenic scores of environmental sensitivity (PGS-ES) and psychotic-like experiences (PGS-PLE), moderated the impact of early-life positive and negative experiences on trans-syndromic outcomes, including subclinical psychotic features and positive mental health, in a DS manner. PGS and measures of early environmental, psychopathology, positive outcomes, and functioning were collected from 941 nonclinical young adults. A comprehensive factorial analysis of positive and negative environmental measures resulted in a general exposome score and four specific factors. A competitive-confirmatory approach examined DS patterns using LEGIT R package. Individuals with higher PGS-ES reported greater psychopathology, poorer functioning, and lower positive mental health outcomes when exposed to fewer positive experiences or poorer paternal parenting; but also exhibited less symptoms and more positive outcomes when exposed to supportive environments compared to individuals with lower PGS-ES. PGS-PLE only predicted psychopathology in a diathesis-stress manner. Findings support the trans-syndromic validity of the DS model, indicating that genetic susceptibility to the environment operated "for better and for worse" by impacting both ill and positive mental health. This highlights the importance of positive experiences and underscores the need to integrate risk and resilience models in psychosis.

1. Introduction

Research on gene-environment interactions has traditionally been guided by diathesis-stress models that posit that individuals carrying genetic-risk variants are more vulnerable to the effects of adversity and more prone to develop psychopathology.[1] At its core, diathesis-stress is a *disease* model with a focus on dysfunction. Evolutionary theory, however, suggests that some individuals may differ in their susceptibility (or sensitivity) to the *full* spectrum of environmental factors, that is, both adverse and supportive.[2-4] The model of Differential Susceptibility (DS) to the environment posits that individuals traditionally considered to carry greater vulnerability may be better conceptualized as having a greater susceptibility to the environment (i.e., being more plastic or malleable).[5] It is hypothesized that some of the same genetic variants or temperament traits involved in increasing the negative effects of adversity could also enhance the likelihood of benefiting from positive experiences ("for better and for worse").[2] A related model of gene-environment interaction (GxE) is vantage sensitivity,[6] which poses that certain genetic variants may enhance the likelihood of benefiting from positive experiences without implying an increase in the susceptibility to negative experiences. This model is the mirror image of diathesis-stress, and while DS serves as an overarching framework that incorporates the conceptual elements of both diathesis-stress and vantage sensitivity, it remains theoretically distinct. DS is grounded in evolutionary theory and proposes that certain traits confer sensitivity to both positive and negative environmental factors.[7]

A critical difference of DS with disease models such as diathesis-stress is that individuals are not considered as *either* vulnerable or resilient, but rather as more or less responsive to their environment. DS considers that experience-driven plasticity (i.e., mechanisms that enable learning in response to environmental experiences to allow adaptation), often neglected in psychopathology[8], are related to *both* adverse and positive experiences, allowing the integration of causal models that include both risk and resilience. Thus, DS provides conceptual grounding for interventions aimed at enhancing environmental conditions to bolster resilience of highly susceptible individuals, rather than merely perceiving them as vulnerable and focusing on risk reduction.

Despite emerging recognition that many transdiagnostic developmental pathways can lead to psychosis,[9] developmental psychopathology models in psychosis have been historically framed within the diathesis-stress paradigm and focused on the interaction of genetic risk with environmental insults (e.g., obstetric complications) to trigger abnormal neurodevelopmental trajectories leading to risk and symptoms.[10] Research would benefit from broader developmental perspectives that consider the interaction of disorder-specific and unspecific risk factors as well as development-enhancing environmental experiences as proposed by DS, such as: (i) increasing recognition of phenotypic dimensionality that is consistent with evidence that psychosis genetic risk is broadly distributed in the population[11] and associated with multiple disorders,[12] (ii) adverse experiences are strong determinants of psychosis[13] , whereas *positive* experiences can be protective factors (e.g., Butler et al.[14]), and (iii) population studies indicate that genetic and environmental risk for psychosis is associated with positive outcomes, such as exceptional social achievement[15] and creativity[16], converging with robust findings connecting creativity with schizotypy and soft bipolarity.[17-19]

The notion that the *diagnosis* of schizophrenia may be associated with any positive features may seem counterintuitive. However, psychosis is expressed across a dynamic continuum in which schizophrenia represents the most extreme form of a broadly distributed psychosis liability including schizotypy traits and psychotic-like experiences (PLE).[20-23] PLE are also expressed in non-psychotic manifestations such as anxiety or depression,[24] consistent with trans-syndromic models such as the Research Domain of Criteria (RDoC)[25] and the Hierarchical Taxonomy of Psychopathology (HiTOP)[26]. Integrated hierarchical models of psychopathology consider a general psychopathology factor (e.g., p factor)[27] that confers broad risk for symptoms across multiple domains, thus enabling the study of shared risk and protective factors across diagnostic spectra. Nonetheless, the idea that a single dimension can fully capture variation in psychopathology has been challenged.[28] For instance, schizotypy explains much less variance when considering it as a homogeneous unidimensional construct than when examining its dimensions (i.e., positive, negative and disorganized), that have shared yet distinct etiological factors.[23,29]

General models of psychopathology focus on symptom dimensions, but do not integrate key aspects of mental health such as well-being and functioning. The dual-continua model of mental health[30] recognizes psychopathology and well-being as distinct yet interconnected spectra in which mental illness and well-being can coexist. Thus, the absence of psychopathology does not guarantee positive mental health, and individuals with psychological disorders can experience well-being.[31] Similarly, research supports that psychopathology and functioning are different constructs to be investigated separately (e.g., Yang et al.[32]).

Childhood adversity is a key factor for mental illness[33], including psychosis[34] and subclinical psychosis.[35] Recent research suggests that the exposome, the lifetime interconnected network of environmental exposures encountered by an individual,[36, 37] is predictive of a wide range of psychopathological manifestations, including psychosis.[38, 39] The exposome framework takes into consideration correlations among exposures, and it has been shown that an aggregate weighted score (exposome score for schizophrenia) predicts not only psychosis-spectrum disorders, but also general mental health problems and functioning.[40] However, limited studies have examined positive exposures and their potential for resilience in at-risk or affected individuals.[41]

Barrantes-Vidal et al.[42,43] recently conducted a proof-of-concept study on the suitability of DS to the extended psychosis phenotype with nonclinical young adults that supported DS predictions. Participants with higher scores on genetic sensitivity to the environment showed increased subclinical psychosis, depression, and anxiety if they experienced more childhood adversity, but fewer symptoms if they reported less adversity, compared to those with lower genetic sensitivity. Genetic sensitivity was indexed by a Polygenic Score of Environmental Sensitivity (PGS-ES) developed by Keers et al.[44] in a genome-wide study using a twin design. By associating intra-pair differences in emotional problems to genetic variants in genetically identical twins in their study, PGS captures emotional response DS to twins' nonshared environments. Similarly, a PGS specific to psychotic-like experiences (PGS-PLE)[45] moderated the effect of adversity on PLE, positive schizotypy, and depression following the DS model, but only PGS-ES interactions survived correction for multiple testing.[42] Overall, our proof-of-

concept supported the hypothesis that sensitivity to the environment and psychosocial experiences are relevant for multiple outcomes, including the extended psychosis phenotype, in a DS manner.

The Present Study

This study replicates our initial examination of the adequacy of the DS model to the psychosis extended phenotype[42] and extends it by examining a larger sample and specifically assessing *positive* environmental experiences and *positive* mental health outcomes, rather than relying on low adversity and psychopathology scores as proxy indicators of protective environments and positive mental health outcomes, respectively. We used competitive and confirmatory model-testing approaches[46,47] to assess the fit of GxE interactions between PGS-ES and childhood environment to DS, diathesis-stress, and vantage models.

Our main goal was to examine whether individual differences in genetic sensitivity to the environment moderated the impact of early-life adverse and positive experiences in a DS manner on three major outcome domains: (i) subclinical psychopathology, as indexed by a general p-factor encompassing psychosis-spectrum, depressive, and anxiety features; (ii) a positive mental health index; and (iii) general and social functioning. If significant GxE models emerged, we conducted exploratory examinations of the GxE interactions for the individual psychopathology and positive mental health measures. This allowed us to identify which components of the major outcome domains yielded specific GxE patterns. Study hypotheses, methods, and data analytic plan were pre-registered at the Open Science Framework (https://osf.io/ysqa5).

Consistent with DS, we hypothesized that individuals with high genetic susceptibility to the environment would report (i) increased psychopathology and impairment when exposed to adversity and, at the same time, (ii) better functioning and positive mental health when exposed to positive environmental factors and/or low adversity compared to those genetically less sensitive to the environment. Secondarily, we explored whether a PGS specifically related to PLE in nonclinical samples (PGS-PLE) likewise moderated the impact of the full spectrum of environmental experiences on our outcomes in a DS manner. Considering that sensitivity to the environment is probably a nonspecific causative factor of mental health and evidence that PRS-Schizophrenia confers transdiagnostic risk for mental suffering,[48] we hypothesized that part of the variance captured by PGS-PLE relates to a heightened sensitivity to the environment and would thus fit a DS pattern. Lastly, we hypothesized that the positive, but not the negative, dimension of schizotypy, would show DS for both PGS-ES and PGS-PLE, given that the positive dimension of psychosis is related to childhood adversity across subclinical and clinical expressions.[49]

2. Methods

2.1. Participants

The sample consisted of 941 nonclinical participants (M_{age}=23, *SD*=5.9, age range 18-62 years, 96% between 18-35 years, 76% self-reported as female) recruited at two universities in Barcelona recruited by advertisements to students and staff. Exclusion criteria were a) < 18 years-old, and b) having grandparents of non-Spanish origin (required for the ancestry

homogeneity of genetic analyses). Initially, 1220 participants completed our measures, with 39 excluded due to invalid protocols (score > 3 on the Infrequency Scale).[50] From 1181 with valid self-report data, 1014 provided saliva for DNA extraction. After genetic quality control procedures (see supplementary material), the final sample included 941 participants.

All participants provided written informed consent. The study was performed in accordance with the Ethics Committee of the Universitat Autònoma de Barcelona (Comissió d'Ètica en l'Experimentació Animal i Humana, ref. 5426).

2.2. Materials and Procedure

2.2.1. Polygenic Scores (PGS)

DNA was extracted from saliva and genotyped using the Illumina Infinium Global Screening Array v3.0 + MD Chip. GenomeStudio v2.0.4 (Illumina Inc., San Diego, CA, USA). Details on the genotyping, quality control, and imputation procedures are reported in supplementary material.

The PGS-ES was calculated based on Keers and colleagues.[44] For the secondary goal, PGS-PLE was computed based on the Legge et al.'s[45] GWAS for PLE (see results with PGS-PLE in supplementary material). The classical Clumping + Thresholding method with PLINK v1.9 was applied. Independent variants were selected by clumping ($r2<0.1$ within a 1000kb window for PGS-ES and $r2<0.02$ within a 1000 kb window for PGS-PLE) using the 1000 Genomes Project phase 3[51] as a European linkage disequilibrium (LD) reference panel. Consistent with previous evidence using PGS-ES showing most consistent results with higher thresholds of PGS-ES,[42,43,52] we employed scores with *p*-value thresholds of 0.05 and 0.1. For the sake of consistency, the same thresholds were employed for the secondary exploratory analyses with PGS-PLE.

2.2.2. Exposome of Early-Life Experiences

Participants completed the Childhood Trauma Questionnaire-Brief (CTQ-B)[53], the Childhood Experiences of Care and Abuse Questionnaire-3 Brief (CECA.Q-3)[54], the Parental Bonding Instrument (PBI)[55] the Positive Childhood Experiences Scale (PCE)[56], the Benevolent Childhood Experiences Scale (BCE)[57], and 4 items assessing family-level protective factors from Crush et al.[58]

Given content overlap across scales, we conducted (i) successive Exploratory Factor Analyses (EFAs) to eliminate irrelevant or redundant items using Iterative Target Rotation (ITR)[59,60], and (ii) a Bifactor Confirmatory Factor Analysis (BCFA) using the WLSMV estimator to identify a general factor. A total of 145 items were included. Details about the data reduction procedure can be found in Lavín et al.[61] Finally, five factor scores were derived from the BCFA (Figure 1), based on the 94 items retained after the data optimization process. Factor 1 included extra-familiar positive experiences and peer support ("Positive Experiences"); Factor 2 included negative experiences or lack of care related to the paternal figure ("Paternal adversity"); Factor 3 included the same experiences as Factor 2, but for the maternal figure ("Maternal adversity"); and Factor 4 included rarely endorsed experiences such as role reversal and emotional or physical abuse ("Other Adverse Experiences"). Finally, a general factor

included loadings from all variables of the model ("General Exposome Factor"). The final bifactor structure showed excellent fit (e.g., comparative fit index) and good model-based reliability (e.g., H index and omega-hierarchical) (see Lavín et al.[61]).

2.2.3. Phenotypic measures

2.2.3.1 Psychopathology factor (P-factor)

The Multidimensional Schizotypy Scale-Brief (MSS-B)[62] assessed positive (Cronbach's α = .77), negative (α = .70) and disorganized (α = .88) schizotypy dimensions. The Community Assessment of Psychic Experiences (CAPE)[63] assessed positive PLE (α = .83). Due to a technical issue in the data collection software, 4% of participants had missing data for items from the disorganized MSS subscale and the CAPE positive PLE, which were addressed using multiple imputation.[64] The "Bar Procedure"[65] was then applied to compress the multiply imputed SPSS files into a single file by pooling the values for each missing data point. The Ideas of Reference (α = .75) and Suspiciousness (α = .77) subscales of the Schizotypal Personality Questionnaire (SPQ)[66] assessed trait paranoia. Depressive symptoms were measured using the Beck Depression Inventory (BDI; α = .91)[67] and anxiety symptoms were assessed with the Beck Anxiety Inventory (BAI; α = .90).[68]

An EFA using ITR was performed using the measures described above. It revealed that items could be grouped into four distinct factors with some expected cross-loadings.[63] This four-factor configuration was introduced in the subsequent BCFA. The Model's fit was good (CFI = 0.947, TLI = 0.945, RMSEA = 0.047, SRMR = 0.066). Four specific factors capturing Affective Dysregulation, Social/Cognitive Malfunctioning, Positive Schizotypy, and Negative Schizotypy, as well as a general factor, accounting for the shared variance among all variables ("p-factor") were derived.

2.2.3.2. Positive mental health

Three well-established measures were used: the Rosenberg Self-Esteem Scale (RSES; α = .88)[69], the Connor-Davidson Resilience Scale (CD-RISC; α = .84)[70], and the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; α = .91).[71]

A composite measure of positive mental health was obtained performing an EFA with oblimin rotation. Items clustered by measure, yielding a three-factor solution devoid of cross-loadings. To obtain scores for the positive mental health factor this three-factor structure was entered as the basis of the subsequent BCFA. The model exhibited excellent fit indices (CFI: .973; TLI: .970; SRMR: .044; RMSEA: .087).

2.2.3.3. Functioning

The Social Functioning Questionnaire[72] covers aspects of both social and general functioning (α = .62).

2.3. Analytic Plan

First, descriptive and correlational data between study variables were examined to disregard potential gene-environment correlations that could interfere with the interpretation of GxE effects. GxE analyses were conducted using version 3.6.3 of the LEGIT package in R,[73]

which was designed to examine the fit of GxE interactions. Following Belsky & Widaman[47], we first used a standard regression to test the significance of the interaction term. We examined whether the interaction yielded an F > 1, which indicates sufficient variation in the interaction term[47,74] to proceed to the main analytic step, the competitive-confirmatory model testing.[48,75] This approach works by re-parameterizing the crossover point of the interaction to envision weak and strong versions of GxE models: DS, diathesis-stress, and vantage-sensitivity, and it determines which provides the best fit to the data. Moreover, LEGIT incorporates a recent improvement as compared to the original re-parametrization approach,[47] by including re-parameterization of models that do not include the GxE term (intercept only, gene only, environment only, gene and environment only) to examine the fit of these non-GxE models along with the GxE models. The best model fit is evaluated based on the lowest Akaike Information Criterion (AIC)[76] fit index. An interaction is classified as "DS" if this model has a) the lowest AIC, and b) the 95% interval of its estimated crossover point is within observable bounds of the environmental score. However, if any of the four models without the interaction term shows the lowest AIC, the interaction will be considered as showing no evidence of GxE. Of note, as a conservative approach to avoid overinterpreting small differences—and although there is no universally accepted rule—models differing by less than 1 point in AIC will be considered statistically indistinguishable in terms of fit, and both should be considered plausible[77]. Including non-GxE models in the comparison process of re-parametrized models is critical to minimize the rate of false positive findings to 5% or lower. Even if the *F* ratio strategy from the initial regression model already prevents fitting Type I error more than traditional *p* values would,[48] fit indices such as AIC provide a more holistic evaluation of the model by considering both the goodness-of-fit and the simplicity of the model, thus leading to a more robust model selection, especially when multiple models are examined.[76,77]

All analyses included the first two ancestry-informative principal components as covariates in the regression model (see supplementary material) and were trimmed from the subsequent competitive-confirmatory test phase if they were nonsignificant. Finally, resampling procedures including k-fold cross-validation and bootstrapping were conducted to assess model stability and generalizability; details are provided in the Supplementary Materials. The code used for data analysis is available from the corresponding author upon reasonable request.

3. Results

Descriptive statistics and Pearson correlations are in supplementary material (Table S1 and S2). No significant correlations were found between susceptibility factors and environmental or outcome measures, except for small effect size associations between PGS-ES ($p < .10$) and resilience ($r = .07$), and PGS-PLE with PLE ($r = .06$, for threshold $p < .05$), suspiciousness ($r = .07$-08, for thresholds $p < .05$ and $p < .10$ respectively) and ideas of reference ($r = .06$, for threshold $p < .10$).

3.1. PGS-ES as a moderating susceptibility factor

Table 1 shows the results of first step regression models on the three main outcome domains. The analyses revealed an *F* ratio > 1 for the interactions between both thresholds of PGS-ES and Positive Experiences on the p-factor and positive mental health, and Paternal

Adversity on the p-factor and functioning (Table 1), providing support for proceeding to the competitive-confirmatory model testing. Only threshold $p < .05$ of PGS-ES interacted with Other Adverse Experiences on positive mental health and with the General Exposome factor on functioning, and only threshold $p < .10$ of PGS-ES interacted with Maternal Adversity on the p-factor and functioning. These interactions showed F ratios close to 1, whereas those interactions that were significant across the two PGS-ES thresholds exceeded $F > 2$. Please note that main effects of the PGS and environmental predictors are not the focus of the study and thus are reported in Supplementary Table S3.

Table 2 shows the output of the second analytic step, the competitive-confirmatory tests for those interactions that showed an F ratio > 1 in the previous step. Findings revealed that interactions between PGS-ES (threshold $p < .10$) and Positive Experiences on the p-factor and on positive mental health were consistent with a model of DS weak and strong, respectively (Table 2; Figure 2a,b), indicating that participants with higher PGS-ES showed less psychopathology and higher positive mental health when exposed to highly positive experiences but more psychopathology and lower positive mental health when exposed to a less positive environment in childhood, as compared to those with lower PGS-ES. For PGS-ES threshold $p < .05$, these interactions indicated a vantage sensitivity strong model, in which higher PGS-ES showed less psychopathology and more positive mental health when exposed to more positive experiences, but were not affected by lower levels of positive experiences (Table S4). The interaction between PGS-ES and Paternal Adversity on both the p-factor and functioning were consistent with models of DS strong for both PGS-ES thresholds, $p < .05$ (Table S4) and $p < .10$ (Table 2; Figure 2c,d), indicating that individuals with higher PGS-ES displayed more psychopathology and worse functioning when exposed to higher levels of paternal adversity but also less psychopathology and better functioning when exposed to lower levels of paternal adversity, compared to lower PGS-ES individuals. The interaction between PGS-ES ($p < .10$) and Maternal Adversity on the p-factor showed AIC values for the diathesis-stress weak and G+E models differing by less than 1, indicating statistically indistinguishable fit and inconclusive GxE evidence. The interaction between PGS-ES (threshold $p < .05$) and Other Adverse Experiences on positive mental health suggested a weak model of vantage sensitivity and with the General Exposome on functioning fitted an 'E only' model, thus suggesting no evidence for GxE.

Given that the p-factor and the positive mental health factor yielded significant interaction effects, in secondary analyses we examined the interactions for the individual psychopathology and positive mental health measures. As shown in Table 3, findings revealed that both thresholds of PGS-ES specifically moderated the effects of Positive Experiences on disorganized schizotypy, positive PLE, depression, well-being and self-esteem, as well as the relationship between Paternal Adversity and positive schizotypy, disorganized schizotypy, suspiciousness, depression and well-being (Table 3). Subsequent competitive-confirmatory testing (Table 4) revealed that all interactions indicated DS strong models, particularly for PGS-ES threshold $p < .10$. For interactions with threshold $p < .05$ of PGS-ES, the model with lowest AIC was a vantage sensitivity model for positive schizotypy, but in the case of disorganized schizotypy, depression and suspiciousness the AIC indices were in line with the $p < .10$ threshold (Table S6).

4. Discussion

Overall, this study replicates our proof-of-concept examination of the adequacy of the DS model for the psychosis extended phenotype[42,43] and extends it by using a larger sample and including the full spectrum of positive and negative early-life environmental experiences and both negative and positive outcomes. Several findings supported the DS model, as individuals with higher genetic susceptibility to the environment reporting lower levels of positive experiences in childhood or poor paternal parenting showed increased levels of subclinical psychotic and affective symptoms, decreased functioning and lower positive mental health outcomes; at the same time, they displayed fewer symptoms and increased positive outcomes when exposed to supportive childhood environments compared to participants with lower genetic sensitivity. Thus, as hypothesized, individual differences in genetic sensitivity to the environment operated "for better and for worse", impacting both positive and negative outcomes. Thus, the almost exclusive focus on negative environmental exposures constrains our understanding of environmental contributions to risk and resilience, and might account for the heterogeneity of results across studies. Notably, the DS relevance of positive experiences was not restricted to affective symptoms, but was trans-syndromic, applying to positive, paranoid and disorganized psychosis dimensions. This is consistent with the critical role of psychosocial factors in psychosis and shows, for the first time, that genetic susceptibility to the environment moderates *both* adverse and positive experiences. Although the findings require replication, overall, they support the hypothesis that the genetic bases of mental disorders may reflect in part genetic variability in sensitivity to the environment.

The finding that positive environmental factors not only contributed to individuals' positive mental health and thriving but also showed a protective effect for both affective and psychotic-like symptoms is particularly relevant to psychosis research, traditionally focused on negative exposures. Although recent work has demonstrated protective effects of good family environments[14,78] and social support,[79] including close friendships[80] and neighborhood cohesion,[58] in relation to PLE, research is scant regarding *early* positive environmental experiences. Interestingly, epigenetic research points to potential neurobiological mechanisms that may account for the impact of positive environmental experiences on the genome. For example, the oxytocin system, which has been suggested to be central to social behaviors, appears to adjust to environmental cues among other mechanisms through oxytocin receptor (OXTR) gene methylation. Early parental care has been hypothesized to reduce OXTR methylation, which may enhance gene expression and facilitate positive social responses.[81] But the complicated interplay between genes, epigenetics, hormones and human behavior still is largely uncharted territory.[82]

Our nonclinical sample presented greater variance in positive than negative environmental measures, which may have facilitated the detection of DS effects at 'both sides' of the continuum of positive experiences. Of note, the Positive Experiences factor was mostly characterized by peer support during school years,[61] which is critical during late childhood and adolescence. The fact that our sample is mostly in their 20's might have facilitated the recall and appraisal of the salience of experiences with peers.

Paternal Adversity also exhibited trans-syndromic effects and impacted individuals' functioning in a DS manner—in fact, it was the only environmental factor predicting functioning. Thus, for participants with higher genetic susceptibility, paternal experiences had a negative impact when higher levels of adversity existed, but better functioning and less psychopathology when lower adversity and higher care were present. These findings align with recent longitudinal evidence showing that paternal, rather than maternal, care reduced psychiatric symptoms, particularly among individuals with higher environmental sensitivity.[83] Also meta-analytic work has underscored the distinct role of parental behavior in child emotional development, with stronger effects for fathers than mothers.[84] Fathers have an important role in children's social development (e.g., providing social representations of the external world)[85], which may partially explain why social functioning was only affected by paternal behavior. Of note, our sample is 77% female. Research shows differential gender-based parental dynamics in the context of traditional gender roles (e.g., fathers being more authoritarian or strict than mothers,[86] particularly among father-daughter dyads[87]), and gender-specific sensitivity to paternal bonding experiences (e.g., women being more sensitive to paternal caregiving).[88] Maladaptive paternal control tends to have a more detrimental impact on daughters' adjustment than similar maternal behaviors.[89] However, increased father involvement in caregiving is associated with fostering resilience in children's development.[85] These differential effects between maternal and paternal parenting align with the unexpected lack of significant effects of maternal adversity in the present study. One may speculate that optimal maternal behavior is often perceived as a normative aspect of caregiving, and that higher levels of variability may be needed to impact children's psychological distress, compared to paternal behavior. Furthermore, protective effects of positive paternal behavior may serve as a proxy for overall positive family environment. Father engagement in parenting has been associated with decreased maternal burden and stress and, thus, a healthier family dynamic.[90] Although the Paternal Adversity factor includes some positive experiences (with negative loadings on the factor), both Paternal and Maternal Adversity factors assess adversity due to currently available measures, which may limit detection of effects for positive mental health.

As hypothesized, evidence of DS was found for most dimensions of the extended psychosis phenotype except for negative schizotypy, which was not expected to be associated with increased sensitivity as it is characterized by low openness to experience,[91] replicating our initial proof-of-concept study.[41] PGS-ES impacted positive PLE in a DS manner but, unexpectedly, not positive schizotypy. Of note, MSS positive schizotypy had a narrower distribution than CAPE PLE. Despite their overlap, the MSS includes experiences of odd somatic ideation and physical perceptions, not tapped by CAPE, that were less endorsed in our nonclinical sample. The effects of both Positive Experiences and Paternal Adversity were consistently found for the disorganized dimension in a DS manner, supporting the notion that these psychotic-like manifestations are proxy indicators of severity across a mental health severity continuum[48,92] in which a greater sensitivity to the environment, in interaction with environmental insults, would have more impact on these phenotypes. Suspiciousness showed DS specifically to the effects of Paternal Adversity for those with elevated PGS-ES. Excessive parental overprotection has been associated with paranoid symptoms as a form of self-

protection against perceived threats,[93] which may be particularly salient in our predominantly female sample.[86] This association may also underlie evidence of intergenerational transmission of paranoia, as parents with higher levels of paranoia may communicate perceived threats to their children and exhibit overprotective parenting behaviors, thus conveying a sense of danger and prompting development of suspicious ideation.[94]

No significant interactions emerged for the Exposome or Other Adverse Experiences factors—the latter not being surprising as it comprised a mix of experiences, including those with the lowest endorsement (e.g., parental violence, emotional abuse and physical abuse). The general exposome factor is adversity-driven and reflects methodological constraints in combining valenced experiences. Positive and negative exposures likely represent distinct dimensions rather than bipolar opposites, suggesting that aggregated measures may obscure specific effects. The lack of significant interactions between the Exposome and genetic susceptibility may indicate that a cumulative approach to environmental exposures, as opposed to a specific adversity-types approach, may be less effective to capture DS effects. Different effects may operate for the different types of adversities and protective factors.[95] Likewise, the exposome factor encompassed items from factors that yielded significant GxE effects (i.e., Positive Experiences and Paternal Adversity) and items from factors that did not (i.e., Maternal Adversity and Other Adverse Experiences). Our results suggest that a 'net' effect is elusive, that is, a supportive group of friends or positive school environment does not counteract the impact of certain adverse family experiences on the same continuum. Consequently, the detrimental impact of the latter may obscure the potential benefits of the former, and vice versa. Finally, the lack of findings may also be influenced by the nature of the sample, as many college students in this study had low rates of severe childhood adversity. Nonetheless, the exposome approach offers the opportunity to integrate multilevel, multimodal and multidimensional environmental data to adopt a holistic view of environmental experiences.[37] To our knowledge, this is the first study examining DS employing both cumulative and specific approaches, so future studies employing this complementary approach should provide further insights into the potential commonalities and specificities of differential susceptibility to the environment.

The PGS-PLE showed a significant interaction with the Exposome on the p-factor, consistent with the diathesis-stress model, indicating that higher adversity led to more symptoms in individuals with higher PGS-PLE. Zhang & Belsky[96] argue that GWAS-derived scores based on the direct association between genetic variants and the same phenotype to be predicted may not function in a DS fashion, but PGS-PLE was chosen because it was developed from a large UK biobank population sample, unlike clinically derived scores like the schizophrenia polygenic score.[45] The diathesis-stress pattern of PGS-PLE suggests higher vulnerability to risk. The previous proof-of-concept study[44] found some DS effects with PGS-PLE, although not statistically robust, possibly due to differences in sample selection as individuals were oversampled for high schizotypy, whereas the present study used an unselected population.

Several strengths characterize the present study, such as the use of polygenic approaches that show larger cumulative effect sizes and have greater predictive power than candidate-gene studies[96] in DS research. The LEGIT package, used to test DS employing the competitive-

confirmatory approach, has demonstrated good accuracy of correctly assigned patterns of interactions and greater predictive ability as compared to other methods (e.g., Regions of Significance).[73] Essential for DS testing, positive environmental and outcome measures were used. A novel factor-derived approach characterizing the Early Exposome was employed, which allowed testing the impact of an overarching general factor as well as specific factor domains that capture unique aspects of early experiences. Regarding limitations, future replication studies with gender-balanced general population samples as well as clinical samples with longitudinal designs are needed to test generalizability of the present exploratory study's findings. Employing a nonclinical sample enables the investigation of shared mechanisms across the psychosis continuum without the many confounds associated to clinical status such as medication, biographical disruption, self-stigma, comorbidity, severe impairment, etc. Particularly relevant to the research question, the study of nonclinical participants likely allows for a more accurate assessment of protective psychosocial experiences and positive outcomes. Furthermore, studying early nonclinical manifestations can inform risk and protective mechanisms that might ground preventive strategies. Another limitation of this study is its reliance on retrospective self-reports to assess early experiences. However, the reliability and validity of such reports are supported by evidence showing that subjective self-reports of adversity have greater predictive validity for psychopathology than objective or interview-based measures.[97] Most measures ranged from excellent to good reliability, but some presented acceptable and one of them poor reliability (Social Functioning Questionnaire), which might be problematic in terms of replication. Critically, validation of the cross-over interactions requires further observational, ecological momentary assessments, or multi-informant measures[98] randomized experiments.[7]

Conclusion and Implications

The results overall support the trans-syndromic validity of the DS model, which is particularly relevant to psychosis given the historic pessimism about prevention and recovery. Recognizing individual differences (e.g., genetic susceptibility to the environment) in response to adversity and support among affected and at-risk individuals can empower and motivate youth, enhancing therapeutic engagement.[99] The protective role of positive experiences supports incorporating resilience-based prevention programs targeting modifiable factors such as childhood environmental conditions to reduce psychosis. Findings underscore the role of interventions aimed at supportive social networks, which may be particularly beneficial for young people with psychosis.[100] Further genome-exposome research from a DS perspective may facilitate the study of emerging neural mechanistic models[101] on neurodevelopmentally sensitive periods[102] involved in increasing sensitivity to the full environmental spectrum, as well as inform precision medicine[103] to tailor interventions to individuals that differ in their susceptibility to psychopathology or responsiveness to specific therapies.

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Figures and Tables

Table 1. Regression models of Gene-Environment interactions with Polygenic Score of Environmental Sensitivity on main outcome domains (*n*=941).

		Main Outcome Domains								
		Psychopathology Factor (P-factor)			Positive Mental Health Factor			Functioning		
G	E	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2
PGS-ES (*p*<.05)	F1 Positive Experiences	**-0.016 (0.009)**$^{+}$	**2.882**	**0.048**	**0.014 (0.009)**	**2.198**	**0.033**	-0.014 (0.038)	0.145	0.058
	F2 Paternal Adversity	**-0.014 (0.008)**$^{+}$	**2.792**	**0.013**	-0.002 (0.009)	0.046	0.008	**0.097 (0.034)****	**7.862**	**0.024**
	F3 Maternal Adversity	-0.007 (0.008)	0.693	0.023	-0.006 (0.009)	0.536	0.009	-0.030 (0.036)	0.684	0.007
	F4 Other Adverse Exp.	-0.001 (0.008)	0.038	0.006	**0.009 (0.009)**	**1.132**	**0.009**	0.029 (0.035)	0.717	0.002
	General Exposome Factor	0.002 (0.007)	0.102	0.191	0.000 (0.007)	0.007	0.160	**0.031 (0.028)**	**1.187**	**0.249**
PGS-ES (*p*<.10)	F1 Positive Experiences	**-0.013 (0.007)**$^{+}$	**3.112**	**0.047**	**0.014 (0.008)**	**3.149**	**0.033**	-0.025 (0.031)	0.618	0.058
	F2 Paternal Adversity	**-0.013 (0.007)**$^{+}$	**3.277**	**0.013**	-0.000 (0.007)	0.008	0.008	**0.073 (0.028)****	**6.692**	**0.022**
	F3 Maternal Adversity	**0.010 (0.008)**	**1.860**	**0.023**	-0.003 (0.008)	0.212	0.008	**-0.035 (0.031)**	**1.301**	**0.007**
	F4 Other Adverse Exp.	-0.001 (0.007)	0.044	0.005	0.004 (0.007)	0.354	0.007	0.022 (0.029)	0.589	0.001
	General Exposome Factor	-0.000 (0.006)	0.007	0.189	0.002 (0.006)	0.118	0.160	0.020 (0.023)	0.727	0.249

[1] Adjusted for ancestry PC1 and PC2.

Notes. Interactions with $F > 1$ are **bolded**.** p<.01, $^{+}$ p<.10. PGS-ES: Polygenic Score of Environmental Sensitivity; Est: Estimate, S.E: Standard Error, Exp: Experiences.

Table 2. Competitive-confirmatory tests of re-parametrized regression models of Polygenic Score of Environmental Sensitivity (p<.10) interactions on main outcome domains (n=941).

PGS-ES (p<.10) x F1 Positive Experiences		**Psychopathology Factor (P-factor)**		**Positive Mental Health Factor**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	2487.72	0.19 (0.06 / 0.31)	**2522.90**	0.01 (-0.14 / 0.16)
	Differential Susceptibility weak	**2487.54**	0.14 (0.02 / 0.26)	2524.20	-0.09 (-0.23 / 0.06)
	Diathesis-stress strong	2512.14	1	2546.99	1
	Diathesis-stress weak	2489.07	1	2527.83	1
	Vantage Sensitivity strong	2514.23	-1	2534.93	-1
	Vantage Sensitivity weak	2488.04	-1	2523.82	-1
Non-GxE models	Intercept only	3142.45	NA	3211.49	NA
	G only	2525.90	NA	2548.04	NA
	E only	3104.63	NA	3177.28	NA
	G+E only	2488.73	NA	2525.40	NA
PGS-ES (p<.10) x F2 Paternal Adversity		**Psychopathology Factor (P-factor)**		**Functioning**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	**2518.90**	-0.20 (-0.38 / -0.02)	**5142.47**	-0.13 (-0.25 / -0.01)
	Differential Susceptibility weak	2520.85	-0.19 (-0.37 / 0)	5144.42	-0.13 (-0.25 / -0.01)
	Diathesis-stress strong	2525.46	1	5158.06	1
	Diathesis-stress weak	2522.28	1	5149.02	1
	Vantage Sensitivity strong	2522.02	-1	5154.56	-1
	Vantage Sensitivity weak	2521.05	-1	5147.86	-1
Non-GxE models	Intercept only	3142.45	NA	5159.41	NA
	G only	2525.90	NA	5161.34	NA
	E only	3136.67	NA	5147.11	NA
	G+E only	2521.92	NA	5148.98	NA
PGS-ES (p<.10) x F3 Maternal Adversity		**Psychopathology Factor (P-factor)**		**Functioning**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	2518.83	-0.21 (-0.40 / -0.02)	5161.05	-0.20 (-0.58 / 0.17)
	Differential Susceptibility weak	2511.38	0.01 (-0.13 / 0.14)	5158.70	-0.04 (-0.27 / 0.18)
	Diathesis-stress strong	2525.52	1	5161.22	1
	Diathesis-stress weak	**2510.75**	1	5157.82	1
	Vantage Sensitivity strong	2525.04	-1	5160.38	-1

	Vantage Sensitivity weak	2511.47	-1	5158.10	-1
Non-GxE models	Intercept only	3142.45	NA	5159.41	NA
	G only	2525.90	NA	5161.34	NA
	E only	3124.88	NA	**5156.10**	NA
	G+E only	2511.16	NA	5158.02	NA

Note. In **bold**, models with lowest AIC. Following Belsky & Widaman (2018), only models with $F > 1$ in the previous analytic step (Table 1) are examined.

Table 3. Regression models of Gene-Environment interactions with Polygenic Score of Environmental Sensitivity on individual measures (*n*=941).

		Psychosis Extended Phenotype								
		Positive Schizotypy			**Negative Schizotypy**			**Disorganized Schizotypy**		
G	**E**	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2
PGS-ES	F1 Positive Experiences	-0.009 (0.029)	0.094	0.006	0.007 (0.022)	0.120	0.039	**-0.066 (0.036)**	**3.281**	**0.041**
(*p*<.05)	F2 Paternal Adversity	**-0.050 (0.025)**$^{+}$	**3.781**	**0.008**	0.015 (0.020)	0.538	0.002	**-0.050 (0.033)**	**2.229**	**0.009**
PGS-ES	F1 Positive Experiences	-0.001 (0.024)	0.038	0.006	-0.008 (0.018)	0.183	0.039	**-0.052 (0.030)**$^{+}$	**2.943**	**0.039**
(*p*<.10)	F2 Paternal Adversity	**-0.035 (0.021)**$^{+}$	**2.870**	**0.007**	0.000 (0.016)	0.000	0.001	**-0.038 (0.027)**	**2.020**	**0.007**
		Psychosis Extended Phenotype								
		Positive PLE			**Suspiciousness**			**Ideas of Reference**		
G	**E**	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2
PGS-ES	F1 Positive Experiences	**-0.086 (0.067)**	**1.647**	**0.011**	-0.011 (0.023)	0.206	0.044	-0.006 (0.025)	0.065	0.011
(*p*<.05)	F2 Paternal Adversity	-0.010 (0.060)	0.026	0.008	**-0.041 (0.021)**$^{+}$	**3.771**	**0.015**	-0.004 (0.022)	0.029	0.008
PGS-ES	F1 Positive Experiences	**-0.067 (0.056)**	**1.468**	**0.011**	-0.009 (0.019)	0.222	0.043	-0.006 (0.021)	0.087	0.011
(*p*<.10)	F2 Paternal Adversity	-0.021 (0.049)	0.188	0.008	**-0.027 (0.017)**	**2.502**	**0.012**	-0.012 (0.018)	0.434	0.008
		Affective Dysregulation								
		Depression			**Anxiety**					
G	**E**	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2			
PGS-ES	F1 Positive Experiences	**-0.164 (0.106)**	**2.409**	**0.037**	-0.046 (0.097)	0.223	0.019			
(*p*<.05)	F2 Paternal Adversity	**-0.167 (0.095)**$^{+}$	**3.072**	**0.014**	-0.081 (0.087)	0.864	0.004			
PGS-ES	F1 Positive Experiences	**-0.138 (0.088)**	**2.478**	**0.037**	-0.004 (0.080)	0.003	0.018			
(*p*<.10)	F2 Paternal Adversity	**-0.138 (0.078)**$^{+}$	**3.117**	**0.014**	-0.046 (0.071)	0.413	0.004			
		Positive Mental Health								
		Well-being			**Self-esteem**			**Resilience**		
G	**E**	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2	Est. (S.E.) [1]	F	R^2
PGS-ES	F1 Positive Experiences	**0.109 (0.099)**	**1.225**	**0.027**	**0.120 (0.061)***	**3.878**	**0.034**	0.062 (0.071)	0.765	0.029
(*p*<.05)	F2 Paternal Adversity	**0.108 (0.089)**	**1.459**	**0.008**	-0.020 (0.055)	0.131	0.006	-0.021 (0.064)	0.108	0.011
PGS-ES	F1 Positive Experiences	**0.117 (0.082)**	**2.026**	**0.027**	**0.110 (0.051)***	**4.716**	**0.037**	0.038 (0.059)	0.404	0.027
(p<.10)	F2 Paternal Adversity	**0.131 (0.073)**$^{+}$	**3.242**	**0.010**	0.005 (0.045)	0.012	0.007	-0.019 (0.052)	0.141	0.010

[1] Adjusted for ancestry PC1 and PC2.

Notes. Interactions with $F > 1$ are **bolded**.** p<.01, $^{+}$ p<.10. PGS-ES: Polygenic Score of Environmental Sensitivity; Est: Estimate, S.E: Standard Error.

Table 4. Competitive-confirmatory tests of re-parametrized regression models of Polygenic Score of Environmental Sensitivity (p<.10) interactions on individual measures (n=941).

PGS-ES (p<.10) x F1 Positive Experiences		**Positive PLE**		**Disorganized Schizotypy**		**Depression**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	**6157.50**	0.23 (-0.05 / 0.51)	**5019.42**	0.28 (0.15 / 0.41)	**7026.13**	0.24 (0.09 / 0.39)
	Differential Susceptibility weak	6159.48	0.23 (-0.05 / 0.51)	5019.81	0.30 (0.17 / 0.43)	7027.03	0.23 (0.08 / 0.38)
	Diathesis-stress strong	6160.13	1	5035.16	1	7039.81	1
	Diathesis-stress weak	6158.81	1	5020.01	1	7027.32	1
	Vantage Sensitivity strong	6161.51	-1	5045.82	-1	7045.05	-1
	Vantage Sensitivity weak	6158.83	-1	5020.87	-1	7027.38	-1
Non-GxE models	Intercept only	7705.63	NA	6339.93	NA	8826.45	NA
	G only	6163.42	NA	5051.88	NA	7051.31	NA
	E only	7703.66	NA	6314.62	NA	8795.7	NA
	G+E only	6158.97	NA	5020.82	NA	7027.61	NA
		Well-being		**Self-esteem**			
		AIC	Crossover point (95%)	AIC	Crossover point (95%)		
GxE models	Differential Susceptibility strong	**6898.93**	0.31 (0.14 / 0.48)	**5992.53**	-0.02 (-0.16 / 0.12)		
	Differential Susceptibility weak	6900.15	0.35 (0.18 / 0.52)	5994.26	-0.08 (-0.22 / 0.07)		
	Diathesis-stress strong	6906.80	1	6021.04	1		
	Diathesis-stress weak	6899.48	1	6000.53	1		
	Vantage Sensitivity strong	6915.28	-1	6004.96	-1		
	Vantage Sensitivity weak	6900.45	-1	5994.72	-1		
Non-GxE models	Intercept only	8675.27	NA	7552.77	NA		
	G only	6918.10	NA	6020.29	NA		
	E only	8648.27	NA	7520.38	NA		
	G+E only	6900.25	NA	5997.04	NA		
PGS-ES (p<.10) x F2 Paternal Adversity		**Positive Schizotypy**		**Disorganized Schizotypy**		**Suspiciousness**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	4556.42	-0.32 (-0.68 / 0.05)	**5048.26**	-0.02 (-0.26 / 0.21)	**4216.52**	-0.41 (-0.62 / -0.20)
	Differential Susceptibility weak	4557.47	-0.20 (-0.51 / 0.11)	5050.22	-0.03 (-0.26 / 0.20)	4218.47	-0.37 (-0.59 / -0.16)
	Diathesis-stress strong	4557.07	1	5050.15	1	4223.32	1
	Diathesis-stress weak	4558.45	1	5049.87	1	4219.92	1
	Vantage Sensitivity strong	**4555.37**	-1	5051.01	-1	4216.58	-1

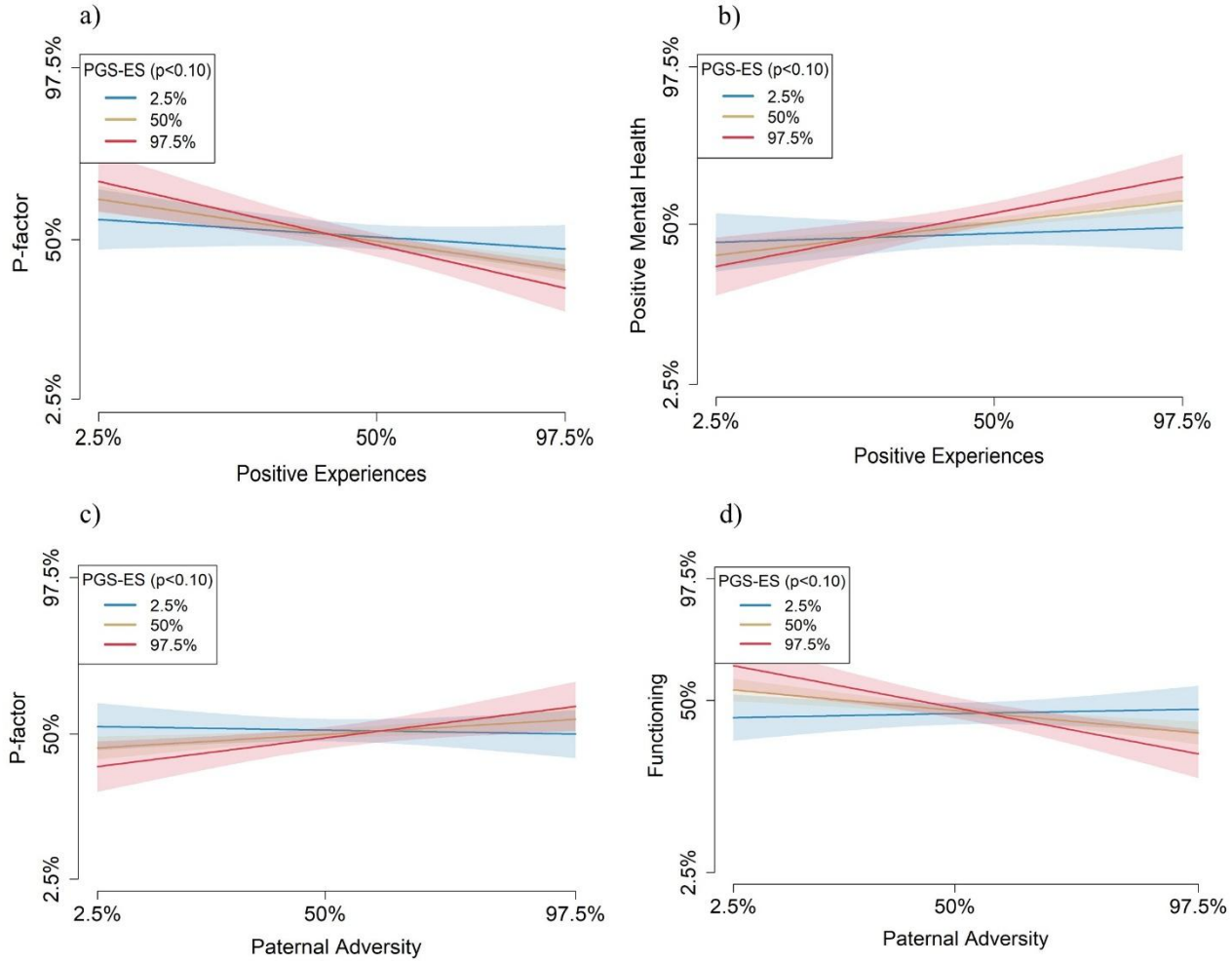
	Vantage Sensitivity weak	4557.31	-1	5050.21	-1	4217.45	-1
Non-GxE models	Intercept only	5679.11	NA	6339.93	NA	5286.46	NA
	G only	4556.73	NA	5051.88	NA	4221.22	NA
	E only	5680.60	NA	6336.22	NA	5284.26	NA
	G+E only	4558.10	NA	5050.17	NA	4218.78	NA
		Depression		**Well-being**			
		AIC	Crossover point (95%)	AIC	Crossover point (95%)		
GxE models	Differential Susceptibility strong	**7048.21**	-0.11 (-0.36 / 0.13)	**6914.12**	0.01 (-0.21 / 0.24)		
	Differential Susceptibility weak	7049.86	-0.10 (-0.34 / 0.13)	6915.72	-0.02 (-0.23 / 0.20)		
	Diathesis-stress strong	7050.37	1	6915.98	1		
	Diathesis-stress weak	7050.57	1	6916.4	1		
	Vantage Sensitivity strong	7049.78	-1	6917.54	-1		
	Vantage Sensitivity weak	7050.32	-1	6917.15	-1		
Non-GxE models	Intercept only	8826.45	NA	8675.27	NA		
	G only	7051.31	NA	6918.10	NA		
	E only	8824.86	NA	8672.20	NA		
	G+E only	7050.67	NA	6916.99	NA		

Note. In **bold**, models with lowest AIC. Following Belsky & Widaman (2018), only models with $F > 1$ in the previous analytic step (Table 3) are examined.

Figure 1. Representation of the top 6 items loading on the specific factors of the Exposome bifactor model. – *See Figure 1 in Chapter 1.*

Adapted from Lavín et al.[61]. Note that while the model included a total of 94 items, the figure displays only the 6 items with the highest loadings on each specific factor for clarity.

Figure 2. Interactions PGS-ES (p<.10) with F > 1 on main outcome domains.



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Chapter 4

Genetic Sensitivity to the Environment Moderates the Impact of Positive and Negative Childhood Experiences on Psychological Adjustment "For Good and for Bad"

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Abstract

Background: The vulnerability-stress framework guiding gene-environment interaction (GxE) research overlooks the role of positive experiences. The Differential Susceptibility (DS) model offers a broader perspective, suggesting that individuals vary in sensitivity to *both* negative and positive environments. This study aimed at replicating previous DS research by examining interactions between Polygenic Scores for Environmental Sensitivity (PGS-ES) and positive and negative early exposures on subclinical psychosis and internalizing psychopathology, functioning, and wellbeing.

Methods: The sample consisted of 638 twins from the first wave of the TwinssCan study, a general population twin cohort. PGS-ES and adversity, bullying and positive experiences in childhood were collected, along with assessments of psychotic, affective, functioning and positive mental health. GxE interactions were tested under a competitive-confirmatory approach.

Results: DS effects were found for the interactions between PGS-ES and all environmental exposures on schizotypic eccentricity and functioning. Adolescents with high genetic sensitivity were rated as more eccentric and less functional under childhood adversity, but were rated as less eccentric and better adjusted under childhood favorable conditions. DS also resulted from the interaction between PGS-ES and positive childhood on social coping. No significant models emerged for internalizing or wellbeing.

Conclusion: Findings overall supported DS, indicating that genetic sensitivity to the environment operates in a "for better and for worse" manner depending on the quality of environmental exposures. It extends initial evidence that DS applies to nonclinical psychosis expression and highlights the importance of considering the full spectrum of environmental conditions to understand both risk and opportunity factors in GxE.

1. Introduction

Gene-by-environment (GxE) research has traditionally followed the diathesis- or vulnerability-stress model, which posits that individuals carrying genetic-risk variants are more vulnerable to adversity and thus more prone to psychopathology [1]. In this framework, adversity is merely a trigger for psychopathology in genetically susceptible individuals. While insightful, the model is incomplete, focusing on negative influences and neglecting positive experiences that foster resilience and well-being [2]. From an evolutionary viewpoint, it is unlikely that natural selection would favor genes that solely increase vulnerability to disorders [3]. In contrast, the Differential Susceptibility (DS) model [3–6] proposes that individuals differ in their sensitivity to both adverse and supportive environments. Thus, some of the same genetic variants and traits increasing vulnerability are presumed to also enhance benefits from positive experiences ("*for better and for worse*") [4]. A third model within the DS framework, is vantage sensitivity, which proposes that certain genetic variants increase sensitivity to positive experiences without heightening vulnerability to negative ones. This model represents the mirror image of vulnerability–stress, whereas DS provides an overarching framework that integrates elements of both [7, 8].

Unlike disease models such as vulnerability-stress, which categorizes individuals as *either* vulnerable or resilient depending on adversity exposure, the DS model conceptualizes them as more or less responsive to their environment [3]. This challenges the prevailing focus on negative exposures in GxE research, which may distort our understanding of environmental impacts on risk and opportunity factors. In fact, the simultaneous consideration of positive and negative exposures may help explain inconsistencies and replication issues in GxE research [9].

The DS model emerged in the field of developmental psychopathology, and its application to adult and "non-affective" samples remains limited. Traditional GxE approaches to psychosis have focused on genetic *risk* and environmental *insults* as triggers of neurodevelopmental disruptions [10]. However, several advances call for a broader developmental approach to psychosis that considers, consistent with DS, the interaction between non-specific factors (variability factors) with both risk and opportunity outcome-specific factors--as put forward by Szöke et al. [11] in the Variability and Risk Model for Schizophrenia. Such advances include evidence supporting that: (i) psychosis phenotypic dimensionality aligns with findings of a wide distribution of genetic risk in the population [12] that is also linked to several psychopathology manifestations [13], (ii) adversity is a predictor of psychosis [14] but supportive experiences can serve as protective factors [15], and (iii) both genetic and environmental risk factors for psychosis are also associated with positive outcomes [16].

Following this rationale, the Barcelona Longitudinal Investigation of Schizotypy Study [17] (BLISS-1) extended DS research to the psychosis extended phenotype employing Polygenic Scores of Environmental Sensitivity [18] (PGS-ES). PGS-ES indexes genetic sensitivity based on a GWAS that used a monozygotic twin design to identify genetic variants associated with intra-pair differences in internalizing (anxiety and depressive)

symptoms. Because monozygotic twins share the same genome and largely the same family environment, these intra-pair absolute differences in emotional symptom scores can be attributed to differential responses to nonshared environmental experiences. Findings showed that nonclinical young adults with high PGS-ES had more positive schizotypy, Psychotic-Like Experiences (PLE), depression, and anxiety if exposed to childhood adversity, but *fewer* symptoms under low adversity. In a larger independent nonclinical sample encompassing *both* negative and positive early experiences, these findings were replicated and extended to positive outcomes specifically to well-being (BLISS-2) [19] Similar effects were observed testing DS to context in daily-life using Experience Sampling Methodology: participants with high PGS-ES reported more paranoia and negative affect (and less positive affect) after exposure to less-positive contexts, but showed opposite effects after exposure to positive ones [20].

The Present Study

The present study aimed to extend initial findings supporting DS in relation to the psychosis extended phenotype by testing the interaction between PGS-ES and positive and negative experiences on four major outcome domains: (i) psychotic, (ii) internalizing, (iii) functioning, and (iv) positive mental health in the TwinssCan cohort.

It was expected that PGS-ES would moderate associations of both adverse and positive exposures with all outcomes in a DS pattern. High-sensitivity individuals were expected to show more symptoms, worse adaptation, and less well-being under adversity, and the reverse under positive conditions ("for better and for worse"). Furthermore, it was hypothesized that the positive, not negative, schizotypy dimension would show a DS pattern for PGS-ES given its stronger association with psychosocial factors [21]−whereas the negative dimension is characterized by diminished openness to experience.

2. Methods

2.1. Participants

The total sample consisted of 778 twins of which 638 provided genetic data (mean age = 17.36, SD = 3.60; 60.5% female). All participants' ethnicity was White-Caucasian to ensure genetic homogeneity for PGS calculation. Demographic data were obtained through self-report. This final sample consisted of 204 monozygotic twin individuals and 436 dizygotic twin individuals (320 twin pairs). Data were derived from the first wave of the TwinssCan study, a general population twin cohort recruited from the prospective population-based registry East Flanders Prospective Twin Survey (EFPTS) in East Flanders, Belgium. TwinssCan cohort included adolescent and young adult (age range upon enrollment = 15–35 years) twins (n = 796) a, their siblings (n = 43), and parents (n = 363) assessed between April 2010 and April 2014 [22]. For the present study, siblings were excluded to maintain twin-sample homogeneity and to enable multilevel modeling that accounts for intra-pair variation. Written informed consent was obtained from all participants. Exclusion criteria were: lack of parental or caregiver consent for those under 18 years old and having a pervasive mental disorder. The study was approved by the local

ethics committee (Commissie Medische Ethiek van de Universitaire Ziekenhuizen KU Leuven, Nr. B32220107766).

2.2. Polygenic Scores of Environmental Sensitivity

Genotypes were generated on two platforms: the Infinium CoreExome-24 and Infinium PsychArray-24 kits. Details about the genotyping, quality control and imputating procedure can be found in Supplementary Appendix 1. PGS-ES was calculated based on the GWAS for environmental sensitivity [18]. We employed the clumping and threshold methods using PRSice2 [23]. To calculate PGS, the beta-values, effective allele, and P-values were extracted from summary statistics. Insertions and deletions, ambiguous SNPs, SNPs with a MAF < 0.01 and/or imputation quality R^2 < 0.9, as well as SNPs located in complex-LD regions and long-range LD regions [24] (see Supplementary Table 1) were excluded from TwinssCan dataset. Overlapping SNPs between GWAS summary statistics (training dataset), 1000 genomes (reference), and our TwinssCan dataset (target) were selected. These SNPs were clumped in two rounds using PLINK's clump function (round 1: --clump-kb 250 --clump-r2 0.5; round 2: --clump-kb 5000 --clump-r2 0.2). The number of alleles for PGS are listed in Supplementary Table 2. PGS were calculated using PRSice2 [23] at several *p*-value thresholds but scores with *p*-value thresholds of p < 0.10 were used as previous evidence showed that threshold of .10 explained more variance [17, 19]. More liberal thresholds (e.g., $p < .50$) were avoided due to greater overlap with population admixture, which increases the risk of spurious associations.

2.3. Environmental Measures

Childhood adversity was assessed using the Childhood Trauma Questionnaire-Brief (CTQ-B) [25], a 28-item self-report measuring sexual, physical, and emotional abuse, as well as physical and emotional neglect before age 18. To capture experiences not covered by the CTQ-B, 13 questions adapted from the Childhood Experience of Care and Abuse interview [26] were included, addressing adversity in two age periods: 0–11 and 12–17 years. The total sum of endorsed experiences was added to the CTQ score, creating a comprehensive score of childhood adversity.

To assess peer-related adversity, the Retrospective Bullying Questionnaire [27], a self-report measure of childhood and adolescent bullying, was used. Following prior research [28], we selected two items to assess the frequency and intensity of physical, verbal, and indirect bullying in elementary school, along with five items from Part III capturing additional bullying experiences (e.g., "How many times have you skipped school or tried to avoid going to school by doing something?"). The total score reflected the overall exposure to bullying.

To measure positive childhood experiences, a four-item self-report scale (Cronbach's α = .79) assessing upbringing ("I had a very pleasant childhood"), parental relationships ("My parents loved each other very much"), received attention ("I received the attention I needed"), and personal privacy ("My privacy was respected") was used.

2.4. Outcome Measures

2.4.1. Psychosis-spectrum

The SIS-R is a semi-structured interview assessing 20 schizotypal traits and symptoms and 11 signs [29]. In this study, 11 traits/symptoms and 4 signs were rated. Symptoms, such as magical ideation and referential thinking, were based on verbal responses, whereas signs, like goal-directed thinking and affect flatness, were behaviorally assessed. Positive (referential thinking, suspiciousness, magical ideation, illusions, psychotic symptoms and derealization/depersonalization, hypersensitivity) and negative (social isolation, introversion, restricted affect) symptom sum scores were calculated. Schizotypic signs were analyzed separately, as they capture a mixture of positive, negative and disorganized schizotypy dimensions (goal-directedness of thinking, loosening of associations, poverty of speech and eccentricity), and (i) it is well-established that combining different dimensions into composite scores reduces predictive power [30], and (ii) we had an a priori hypothesis regarding the relevance of our genetic predictor specifically for positive features [21]. Additionally, the Positive subscale of the Community Assessment of Psychic Experiences (CAPE) [31] was used to assess the frequency of positive psychotic-like experiences (PLE), providing a self-reported, subjective, evaluation of these experiences that complemented the observer-based SIS-R ratings. The Negative subscale was not included given that prior work in nonclinical samples indicates that it substantially overlaps with the depressive dimension [e.g., 32], and because our hypothesis was specifically focused on positive psychotic-like phenomenology.

2.4.2. Internalizing symptoms

The Symptom Checklist 90 Revised [33] (SCL-90-R) and the depressive subscale of the CAPE [31] were used to assess internalizing symptoms. From the SCL-90-R's nine dimensions, we included depression, anxiety, phobic anxiety, interpersonal sensitivity, somatization, obsessive-compulsive scales and seven additional items reflecting affective dysfunction (e.g., restless or disturbed sleep). The SCL hostility subscale was excluded, as it is conceptually more closely related with externalizing behaviors. Given strong correlations (see Supplementary Table 3) among these variables, a composite internalizing symptoms score was created to streamline analysis and minimize multiple testing. See Supplementary Appendix 2 for a detailed description of the process.

2.4.3. Functioning

Functioning was assessed using the Global Assessment of Functioning scale [34], a standard rating scale that assesses social, occupational, and psychological functioning. Higher scores reflect better functioning.

2.4.4. Positive mental health outcomes

Self-esteem was measured using the Rosenberg Self-Esteem Scale [35], and well-being with the Amsterdamse Psychological Well Being scale [36] (AWS), a 54-item self-rating inventory assessing six dimensions: environmental mastery, purpose in life, self-acceptance, autonomy, personal growth, and personal relationships. Due to strong

correlations among these variables (see Supplementary Table 5), a composite score was created (see SA2 for details).

General coping style was assessed using the Utrecht Coping List [37], which measures seven coping styles: active tackling, avoidance, comforting thoughts, expressing emotions, palliative reaction, passive reaction, and social support. To achieve a broader characterization of coping strategies and optimize the analyses, we examined its factor structure. This process yielded two distinct factors—Active and Passive Coping—whereas the Social Coping subscale was retained as a separate component. See SA2 for details.

2.5. Statistical Analysis

Given the hierarchical structure of the data, with participants nested within twin pairs, linear mixed models were used to account for within-subject clustering of multiple observations of those who were part of the same twin pair. Analyses were conducted using version 3.6.3 of the LEGIT package in R [38], which is specifically designed to examine the fit of GxE interactions. Following Belsky & Widaman [39], we first used a standard regression model to check whether the interaction term yielded significant effects. Specifically, we examined whether the interaction yielded an $F > 1$, which indicates sufficient variation in the interaction term [39] to proceed to the subsequent competitive-confirmatory model testing [40].

The competitive-confirmatory approach works by re-parameterizing the interaction model. That is, it systematically varies the parameters included in the regression equation to compare alternative GxE models. Specifically, this approach contrasts weak and strong versions of the DS, vulnerability-stress, and vantage-sensitivity models and determines which provides the best fit to the data [40]. Moreover, LEGIT incorporates a recent improvement as compared to the original re-parametrization approach, by including re-parameterization of models that do not include the GxE term (intercept only, gene only, environment only, and gene and environment only) to examine the fit of these non-GxE models along with the GxE models. The best model fit is evaluated based on the lowest Akaike Information Criterion (AIC) fit index. An interaction is classified as "DS" if this model has a) the lowest AIC, and b) the 95% interval of its estimated crossover point is within observable bounds of the environmental score. However, if any of the four models without the interaction term shows the lowest AIC, the interaction will be considered as showing no evidence of GxE. Importantly, including non-GxE models in the comparison process of re-parametrized models is critical to minimize the rate of false positive findings to 5% or lower. Furthermore, the accuracy and predictive ability of the competitive-confirmatory model testing with LEGIT as compared to other methods such as the classic Regions of Significance has been documented [38].

All analyses included the first two ancestry-informative principal components (PC1 and PC2) as covariates [41] in the regression model and were trimmed from the subsequent competitive-confirmatory test phase if they were nonsignificant.

3. Results

For the psychosis phenotype, only eccentricity was predicted by the interaction between PGS-ES and all environmental variables (adverse, positive and bullying), with $F > 1$ (Table 1). Competitive-confirmatory tests revealed that interactions between PGS-ES and adverse and positive experiences fitted a strong DS model (Table 2, 3). That is, those with higher PGS-ES showed more eccentricity if exposed to adverse or less positive environments, but decreased eccentricity if exposed to highly positive environments (or low adversity), compared to those with lower PGS-ES (Figure 1a, 1d). Regarding the interaction with bullying, the competitive-confirmatory test revealed similar AIC indices between a DS and an E only model, indicating inconclusive findings about GxE (Table 4; Figure 1g).

PGS-ES interacted with adverse childhood on positive PLE (Table 1), although the AIC indices from the competitive-confirmatory testing indicated that the interaction fitted very similarly either a model of G+E only (that is, both the PGS-ES and the environment show main effects) or a DS model, indicating inconclusive findings about GxE (Table 2).

Functioning emerged as a significant outcome of the interaction between PGS-ES and the three environmental factors (Table 1) consistent with DS (Figure 1b, 1e, 1h), indicating that those with high PGS-ES showed decreased functioning when exposed to an adverse or less positive environment but increased functioning when exposed to highly positive environments (or absence of adversity) (Tables 2, 4). Only the interaction between PGS-ES and positive childhood revealed similar fit for both, a DS and a weak vulnerability-stress model, indicating that the effects could fit both (Table 3).

Regarding coping styles, PGS-ES showed interaction effects ($F > 1$) with both adverse and positive childhood on passive and social coping. Active coping also showed $F > 1$, but only for the interaction with adverse childhood (Table 1). From these, the interaction between PGS-ES and adverse childhood on active coping revealed similar fit indices for both, a DS model and an environment only model (Table 2), while the interaction between PGS-ES and positive childhood on social coping style clearly fitted a DS model (Table 3), indicating that high-PGS-ES individuals showed increased social coping when exposed to high levels of positive childhood experiences, but decreased social strategies when exposed to lower positive influences. The other effects on coping styles were not supported by the competitive-confirmatory test as GxE models.

Finally, no significant GxE interactions were found for internalizing symptoms nor wellbeing.

4. Discussion

Consistent with the DS model, youngsters with high genetic sensitivity to the environment were not only more vulnerable to unfavorable family and school contexts but also more able to benefit from the absence of adversity and presence of positive experiences compared to those with low genetic sensitivity. A conventional GxE analysis under the vulnerability-stress model could only detect increased vulnerability and maladjustment in highly-sensitive individuals and thus might miss the full picture: that the *same* sensitivity also conferred advantages in supportive environments. Notably, all significant GxE

interactions displayed a DS pattern, emerging in general functioning and positive schizotypy traits like eccentricity, aligning with earlier DS findings in nonclinical youth [17, 19, 20]. The relevance of genetic sensitivity in moderating the impact of different types of environmental factors on psychological adjustment underscores the need to examine individual differences in the response to environmental exposures. Also, these results highlight the importance of assessing the full spectrum of environmental conditions when examining GxE, as the coexistence (or compensating effects of) protective factors along with adversity might account for part of the heterogeneity of GxE research. This is particularly relevant for youth mental health as stigma and self-stigma can shape trajectories of risk and/or resilience [42]. Misinterpreting sensitivity to the environment as indexing only risk might severely jeopardize the potential for developmental enhancement and resilience under supportive conditions.

DS effects were consistently detected across the three environmental factors examined. The childhood adversity index, primarily reflecting intrafamilial experiences, produced slightly more interactions than school bullying, which is meaningful given the role of early-life rearing experiences. However, most of the sample (70%) was aged 15-16, when experiences of bullying are still occurring and, thus, their full impact might not yet be captured in this age range (in fact, only bullying at primary school could be analyzed as most participants had not yet finished secondary school). Also, the positive experiences index was more limited in scope and items, possibly reducing sensitivity to DS effects.

DS effects were consistently found for the interactions between PGS-ES and the three environmental factors on schizotypic eccentricity and functioning, indicating that interviewers perceived adolescents with high genetic sensitivity to the environment who reported high adversity/low protective experiences as more odd and dysfunctional but, also, less eccentric and better adjusted when exposed to low adversity/high protective experiences as compared to adolescents with low genetic sensitivity. These findings mirror earlier DS studies in youth, where effects were found for functioning and positive—but not negative—schizotypy [17, 19]. While earlier work reported DS effects for CAPE positive experiences [17, 19], this study only found an interaction on CAPE positive experiences that was close to but did not clearly fit DS, suggesting that interviewer ratings of eccentricity might be more precise than self-reports.

An unexpected finding regarding the hypothesized trans-syndromic effect of genetic sensitivity, and contrary to previous studies [17, 19, 20], was the lack of GxE effects for internalizing symptoms. Of note, adolescent twins showed very low endorsement in all anxiety/depression items from the SCL-90-R, probably due to the measure's emphasis on severe symptomatology (e.g., thinking about death or dying, being afraid to leave the house alone) and clinical well-established manifestations [33], which may not be sensitive enough to detect subtle manifestations in nonclinical populations. An additional interpretation could be that the fact that positive schizotypy shows stronger and more consistent DS effects over affective or anxiety manifestations is consistent with a continuum of psychopathology severity [43] in which psychotic-like manifestations index greater deviance and, thus, greater genetic sensitivity in combination with greater adversity may contribute to stronger effects

for such phenotypes, reinforcing their position on the more severe end of the psychopathology spectrum.

Regarding positive outcomes, no DS interactions were found for wellbeing, possibly because the AWS measure assesses constructs (e.g., autonomy, personal growth, purpose in life) that might be underdeveloped in adolescents. In contrast, significant DS effects were found for the interactions between PGS-ES and adverse childhood on active coping and PGS-ES and positive childhood on social coping, although only the latter clearly fitted DS. High-sensitivity individuals lacking positive rearing may struggle with developing social coping strategies, whereas supportive rearing contexts may promote adaptive coping mechanisms [44].

The fact that DS effects were consistently found in relation to adjustment rather than symptom expression aligns with the developmental phase of the study sample. The sample is mostly composed of adolescents aged 15-17, capturing the intersection of developmental vulnerability and heightened sensitivity to sociocultural influences [45], characterized by highly undifferentiated and comorbid symptomatology [46]. This population is central to the emerging youth mental health crisis, driven by profound societal shifts (e.g., intergenerational inequality, financial instability, climate change, impact of unregulated social media) [42]. Some limitations should be acknowledged, including the reliance on self-report questionnaires, which may be influenced by recall errors and subjective biases, although recent meta-analytic evidence suggests that such reports are valid and reliable predictors of mental health outcomes [47], and the limited generalizability of the study to White adolescent populations. Also, future studies could benefit from broadening environmental assessment by incorporating complementary frameworks—ranging from dimensional models that capture specific features of early experiences to more integrative exposome approaches that offer a comprehensive, multifactorial view of environmental influences—as recent work from our group [19] shows that distinct early environmental dimensions differentially interact with genetic sensitivity to shape developmental outcomes. Nonetheless, the findings support a paradigm shift in how we conceptualize risk, vulnerability, and their associated stigma. The same plasticity factors that increase vulnerability also enhance responsiveness to protective factors, presenting a crucial opportunity for targeted prevention efforts. Interventions must prioritize resilience-building and adaptive coping strategies, particularly given the potential for iatrogenic harm in interventions targeting adolescents [48]. Early interventions that embrace a pluripotent approach—addressing shared risk factors and nonspecific symptoms while promoting resilience—are essential.

To conclude, DS was supported, suggesting that genetic sensitivity to the environment operates “for good and for bad” depending on the quality of environmental factors and extended evidence that this is relevant to the psychosis extended phenotype: high-genetic-susceptibility youngsters that showed greater vulnerability to adversity were the same ones that also displayed a higher capacity to benefit from positive environmental influences. This supports that the long-dominant vulnerability-stress is incomplete and potentially misleading, as it primarily emphasizes vulnerability to negative environments. In

contrast, DS offers a broader perspective that contributes to understanding the complexity underlying risk and opportunity factors to mental health. This perspective has the potential to inform evidence-based interventions aimed not only at reducing psychopathology but also at promoting positive mental health, health—an urgent priority in addressing the current youth mental health crisis and, more broadly, in promoting developmental enhancement during this critical life stage.

For supplementary material accompanying this paper, visit cambridge.org/EPA.

Tables and Figures

Table 1. Regression models of Gene-Environment interactions between Polygenic Score of Environmental Sensitivity and Childhood Adverse. Positive and Bullying Experiences.

	PGS-ES x Adverse Childhood		**PGS-ES x Positive Childhood**		**PGS-ES x Bullying**	
	Est. (S.E.)[a]	F	Est. (S.E.)	F	Est. (S.E.)	F
Psychotic dimensions						
CAPE Positive PLE	.009 (.006)	**2.04**	-.001 (.003)	.18	.006(.004)$^{+}$	**2.86**
SIS-R Interview-based symptoms						
Positive symptoms	.022 (.008)**	**7.59**	-.011 (.004)**	**7.58**	.012(.005)*	**5.41**
Negative symptoms	-.012 (.011)	**1.38**	.001 (.005)	.06	.010(.007)	**1.98**
SIS-R Observation-based symptoms						
Eccentricity	.014 (.004)**	**11.59**	-.008 (.002)***	**16.95**	.007(.002)*	**6.28**
Loosening of associations	-.001 (.002)	.26	.000 (.000)	.00	.000(.001)	.07
Focus of attention	.012(.003)***	**13.72**	-.007 (.002)***	**20.67**	.008(.002)***	**14.59**
Poverty speech	.003 (.004)	.66	.000 (.002)	.04	.002(.002)	.82
Internalizing factor	-.016 (.020)	.64	.021 (.011)$^{+}$	**3.79**	-.013(.014)	.90
Functioning	-.539 (.140)***	**14.88**	.191 (.071)**	**7.20**	-.353(.091)***	**14.89**
Wellbeing	.010 (.019)	.25	.000 (.009)	.01	-.001(.001)	.95
Coping styles						
Active	-.046 (.021)*	**4.70**	.000 (.010)	.00	-.005(.014)	.17
Passive	-.051 (.021)*	**5.70**	.019 (.010)$^{+}$	**3.40**	.004(.014)	.08
Social	-.134 (.088)	**2.32**	.116 (.043)**	**7.22**	-.015(.058)	.69

[a] Adjusted for ancestry PC1 and PC2.

Notes. Interactions with $F > 1$ are **bolded**.*** $p<.05$, ** $p<.01$, $^{+}$ $p<.10$. PGS-ES: Polygenic Score of Environmental Sensitivity; Est: Estimate, S.E: Standard Error.

Table 2. Competitive-confirmatory tests of re-parametrized regression models of Polygenic Score of Environmental Sensitivity (p<.10) x Adverse Childhood interactions.

PGS-ES (p<.10) x Adverse Childhood		**Positive PLE**		**Positive Symptoms**		**Negative Symptoms**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	152.62	(0.5 / 0.78)	412.17	(0.54 / 0.87)	754.5	(0.18 / 1.26)
	Differential Susceptibility weak	**98.46**	**(0.34 / 0.52)**	390.71	(0.59 / 0.86)	735.15	(0.45 / 0.87)
	Vulnerability-stress strong	200.51	1	441.3	1	755.76	1
	Vulnerability-stress weak	101.45	1	394.27	1	735.88	1
	Vantage sensitivity strong	203.10	-1	463.21	-1	760.87	-1
	Vantage sensitivity weak	101.07	-1	400.28	-1	739.06	-1
Non-GxE models	Intercept only	216.89	NA	455.66	NA	784.75	NA
	G only	213.96	NA	457.66	NA	786.7	NA
	E only	100.05	NA	**379.46**	**NA**	**723.88**	**NA**
	G+E only	**98.14**	**NA**	381.26	NA	725.67	NA
		Eccentricity		**Focus of Attention**		**Functioning**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	**-400.37**	**(0.56 / 0.92)**	-641.54	(0.41 / 0.93)	3977.65	(0.62 / 0.87)
	Differential Susceptibility weak	-396.26	(0.58 / 0.93)	-635.03	(0.41 / 0.92)	**3957.92**	**(0.67 / 0.88)**
	Vulnerability-stress strong	-388.68	1	-625.02	1	4005.21	1
	Vulnerability-stress weak	-391.69	1	-623.84	1	3962.85	1
	Vantage sensitivity strong	-369.25	-1	-618.35	-1	4040.16	-1
	Vantage sensitivity weak	-382.01	-1	-620.06	-1	3975.67	-1
Non-GxE models	Intercept only	-355.90	NA	**-671.34**	NA	4209.48	NA
	G only	-353.99	NA	-670.10	NA	4209.50	NA
	E only	-378.35	NA	-644.31	NA	3996.94	NA
	G+E only	-376.46	NA	-642.90	NA	3995.70	NA
		Active Coping		**Passive Coping**		**Social Coping**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	1631.74	(0.45 / 0.95)	1662.35	(-0.41 / 1.34)	3377.71	(0.35 / 1.21)
	Differential Susceptibility weak	**1629.63**	**(0.48 / 0.93)**	1631.07	(0.6 / 1)	3376.22	(0.44 / 1.21)
	Vulnerability-stress strong	1642.03	1	1664.44	1	3379.29	1
	Vulnerability-stress weak	1631.77	1	1631.96	1	**3375.61**	**1**
	Vantage sensitivity strong	1651.05	-1	1664.93	-1	3387.88	-1
	Vantage sensitivity weak	1636.08	-1	1639.79	-1	3380.59	-1

Non-GxE models	Intercept only	1668.48	NA	1672.87	NA	3424.99	NA
	G only	1670.37	NA	1672.62	NA	3376.50	NA
	E only	**1629.97**	**NA**	**1626.33**	**NA**	**3375.39**	**NA**
	G+E only	1631.97	NA	**1626.42**	**NA**	3376.50	NA

Note: The environmental variable was reversed to go from higher to lower adversity for consistency with the LEGIT package, which assumes that direction, ensuring standard model label interpretations (i.e., diathesis-stress and vantage sensitivity). Models with the lowest AIC are bolded. Following Belsky & Widaman (2018), only effects with F > 1 in the prior analytic step (Table 1) are examined in this step.

Table 3. Competitive-confirmatory tests of re-parametrized regression models of Polygenic Score of Environmental Sensitivity (p<.10) x Positive Childhood interactions.

PGS-ES (p<.10) x Positive Childhood		Positive Symptoms		Eccentricity		Focus of Attention	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	435.87	(0.37 / 0.79)	**-397.48**	**(0.48 / 0.82)**	-646.23	(0.29 / 0.71)
	Differential Susceptibility weak	435.68	(0.37 / 0.75)	-390.10	(0.48 / 0.82)	-638.52	(0.3 / 0.72)
	Vulnerability-stress strong	446.51	1	-391.47	1	-630.62	1
	Vulnerability-stress weak	438.79	1	-385.20	1	-624.60	1
	Vantage sensitivity strong	461.64	-1	-370.07	-1	-621.86	-1
	Vantage sensitivity weak	442.93	-1	-372.27	-1	-620.81	-1
Non-GxE models	Intercept only	455.66	NA	-355.90	NA	**-671.34**	**NA**
	G only	457.66	NA	-353.99	NA	-670.10	NA
	E only	**422.17**	**NA**	-368.11	NA	-643.42	NA
	G+E only	424.16	NA	-366.11	NA	-642.45	NA
		Internalizing Symptoms		**Functioning**		**Passive Coping**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	**1692.83**	**(-0.27 / 0.5)**	4011.48	(0.5 / 0.84)	1663.12	(-0.59 / 0.83)
	Differential Susceptibility weak	1646.81	(1.05 / 1.36)	**4004.92**	**(0.56 / 0.86)**	1642.12	(0.72 / 1.15)
	Vulnerability-stress strong	1707.51	1	4017.00	1	1665.55	1
	Vulnerability-stress weak	1644.83	1	**4005.30**	**1**	1640.34	1
	Vantage sensitivity strong	1696.77	-1	4039.65	-1	1664.05	-1
	Vantage sensitivity weak	1653.69	-1	4013.2	-1	1647.27	-1
Non-GxE models	Intercept only	1695.00	NA	4209.48	NA	1672.87	NA
	G only	1688.77	NA	4209.50	NA	1672.62	NA
	E only	1641.96	NA	4036.38	NA	1633.46	NA
	G+E only	**1633.34**	**NA**	4037.01	NA	**1632.15**	**NA**
		Social Coping					
		AIC	Crossover point (95%)				
GxE models	Differential Susceptibility strong	**3370.61**	**(0.4 / 0.94)**				
	Differential Susceptibility weak	3370.93	(0.43 / 0.95)				
	Vulnerability-stress strong	3373.34	1				
	Vulnerability-stress weak	3371.62	1				
	Vantage sensitivity strong	3387.76	-1				

	Vantage sensitivity weak	3378.74	-1
Non-GxE models	Intercept only	3424.99	NA
	G only	3426.08	NA
	E only	3371.82	NA
	G+E only	3373.33	NA

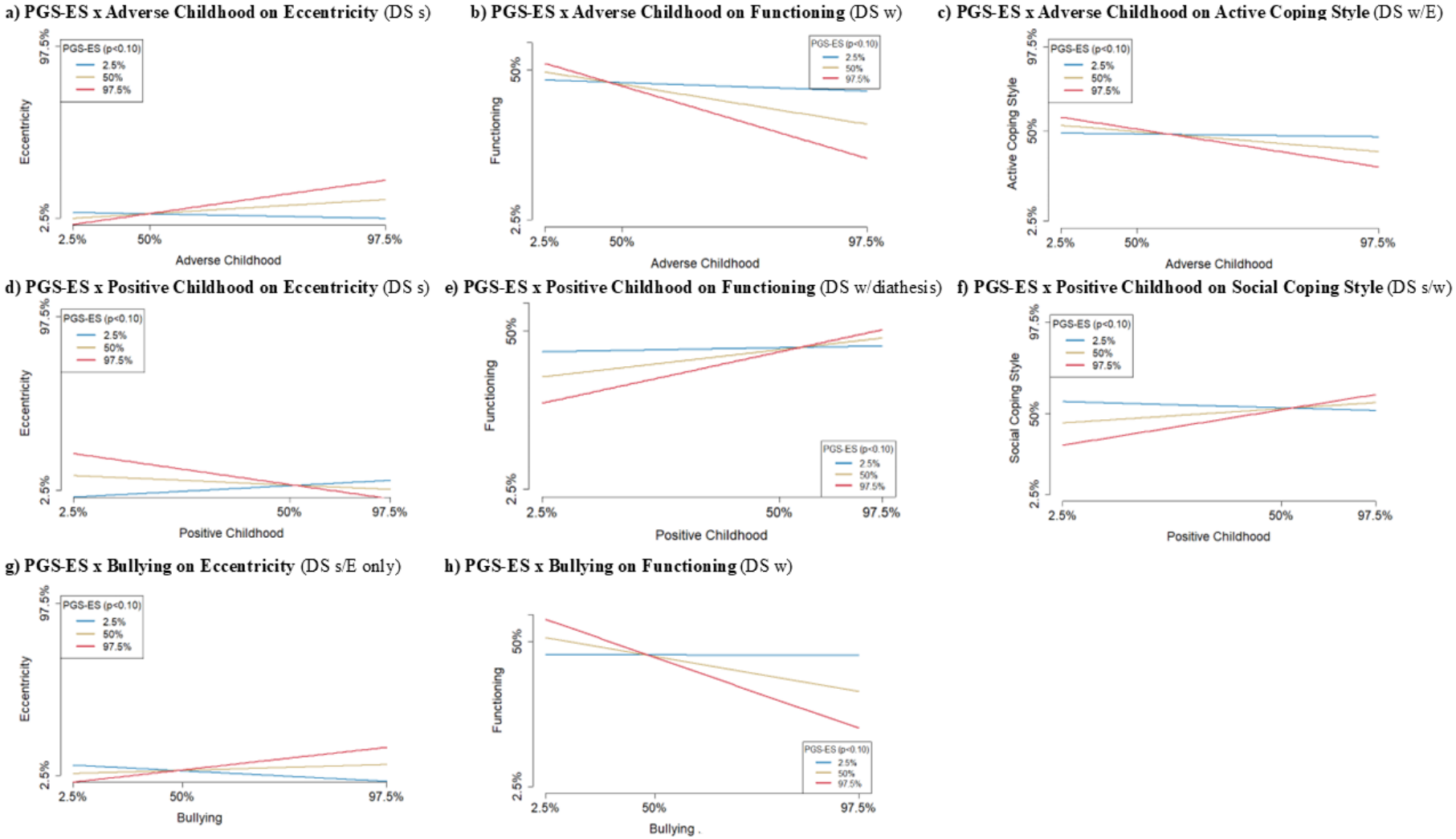
Note: The environmental variable was reversed to go from higher to lower adversity for consistency with the LEGIT package, which assumes that direction, ensuring standard model label interpretations (i.e., diathesis-stress and vantage sensitivity). Models with the lowest AIC are bolded. Following Belsky & Widaman (2018), only effects with F > 1 in the prior analytic step (Table 1) are examined in this step.

Table 4. Competitive-confirmatory tests of re-parametrized regression models of Polygenic Score of Environmental Sensitivity (p<.10) x Bullying interactions.

PGS-ES (p<.10) x Bullying		**Positive PLE**		**Positive Symptoms**		**Negative Symptoms**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	154.64	(0.29 / 0.52)	411.83	(0.39 / 0.65)	746.29	(0.2 / 0.9)
	Differential Susceptibility weak	133.11	(0 / 0.18)	399.67	(0.37 / 0.6)	750.66	(0.22 / 0.89)
	Vulnerability-stress strong	201.92	1	443.82	1	748.96	1
	Vulnerability-stress weak	138.72	1	403.59	1	751.08	1
	Vantage sensitivity strong	197.99	-1	463.91	-1	754.08	-1
	Vantage sensitivity weak	134.62	-1	405.64	-1	753.74	-1
Non-GxE models	Intercept only	216.89	NA	455.66	NA	784.75	NA
	G only	213.96	NA	457.66	NA	786.70	NA
	E only	130.77	NA	**384.30**	**NA**	**733.41**	**NA**
	G+E only	**125.40**	**NA**	386.17	NA	735.38	NA
		Eccentricity		**Focus of Attention**		**Functioning**	
		AIC	Crossover point (95%)	AIC	Crossover point (95%)	AIC	Crossover point (95%)
GxE models	Differential Susceptibility strong	**-390.17**	**(0.35 / 0.88)**	-624.61	(0.16 / 0.72)	3958.04	(0.49 / 0.69)
	Differential Susceptibility weak	-383.36	(0.34 / 0.87)	-620.31	(0.22 / 0.73)	**3948.31**	**(0.53 / 0.72)**
	Vulnerability-stress strong	-387.58	1	-615.21	1	3984.92	1
	Vulnerability-stress weak	-380.90	1	-607.71	1	3954.24	1
	Vantage sensitivity strong	-378.90	-1	-613.04	-1	4022.73	-1
	Vantage sensitivity weak	-375.42	-1	-606.27	-1	3965.03	-1
Non-GxE models	Intercept only	-355.90	NA	**-671.34**	**NA**	4209.48	NA
	G only	-353.99	NA	-670.1	NA	4209.50	NA
	E only	-389.41	NA	-630.51	NA	3977.86	NA
	G+E only	-387.43	NA	-629.34	NA	3978.25	NA

Note: The environmental variable was reversed to go from higher to lower adversity for consistency with the LEGIT package, which assumes that direction, ensuring standard model label interpretations (i.e., diathesis-stress and vantage sensitivity). Models with the lowest AIC are bolded. Following Belsky & Widaman (2018), only effects with F > 1 in the prior analytic step (Table 1) are examined in this step.

Figure 1. Interactions between PGS-ES and Childhood Experiences fitting a Differential Susceptibility model.



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Chapter 5

Polygenic Liability for Schizophrenia, Bipolar and Major Depression Disorders Predicts Differential Susceptibility to Both Positive and Adverse Environments

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To be Submitted

1. Introduction

The emergence and extended application of genome-wide association studies (GWAS) over the past 15 years has allowed the identification of hundreds of genetic variants associated with psychiatric disorders (Abdellaoui et al., 2023; Gandal & Geschwind, 2021), revealing their highly polygenic nature (Goldstein et al., 2009; Visscher et al., 2021) and challenging early expectations in molecular psychiatric genetics that these disorders could be explained by a single or a few genetic variants of large effect (Uher & Zwicker, 2017; Smoller et al., 2019).

Although the genetic architecture varies across disorders (Gandal & Geschwind, 2021), and certain disorder-specific effects have been identified (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019), the growing body of GWAS data has revealed a striking degree of genetic overlap—namely pleiotropy— among many of these conditions. Approximately two-thirds of the genetic variants linked to schizophrenia, bipolar disorder, and major depressive disorder are common to all three (Marsman et al., 2020), with additional overlap extending to neurodevelopmental conditions such as autism spectrum disorder and ADHD (Owen et al., 2025). Additionally, polygenic scores (PGS) for one disorder (e.g., depression) often predict risk for others (e.g., anxiety, PTSD), suggesting shared biological pathways (Keser et al., 2026), a pattern further supported by genomic structural equation modelling (SEM) work identifying a robust higher-order p-factor and a small number of broader genomic factors representing shared signal across 14 psychiatric disorders (Grotzinger et al., 2026).

This 'polygenic paradigm shift' in psychiatric genetics (Owen & O'Donovan, 2021), driven by the discovery of such extreme polygenicity and pleiotropy has further challenged the traditional notion that psychiatric conditions are discrete entities and the categorical nosologies long embedded in clinical practice (Doyle et al., 2025). Nonetheless, the debate around the categoric versus dimensional nature of mental disorders has a longstanding presence in the literature. For instance, high comorbidity rates across disorders (McGrath et al., 2020) and the heterogeneity of symptom profiles within them led to the proposal of a dimensional view of psychosis in the 1990s (Claridge, 1997), building on earlier concepts such as unitary psychosis (*Einheitspsychose*) (Aragona, 2024). According to this view, psychotic disorders exist along a continuum of severity, ranging from personality traits (e.g., schizotypy) and psychotic experiences to personality disorders and psychiatric conditions such as bipolar disorder and schizophrenia, with a gradation of functioning that encloses both adaptive and maladaptive states (Claridge & Barrantes-Vidal, 2011; Kwapil & Barrantes-Vidal, 2015).

This prescient view has been later supported by the notion of psychosis as a transdiagnostic and extended phenotype (van Os & Reininghaus, 2016), supported by evidence that both genetic and environmental risk factors are shared across schizotypy traits (Barrantes-Vidal et al., 2015) and clinical and subclinical psychotic experiences, and that they co-occur and overlap with affective and anxiety symptoms and disorders (van Os et al., 2022). Moreover, longitudinal research has consistently demonstrated heterotypic continuity across mental disorders—with one disorder predicting the later development of another. This pattern has been observed not only in psychosis but also across and within internalizing, externalizing, and

neurodevelopmental domains (Lahey et al., 2014; Shevlin et al., 2017), leading to the development of alternative, dimensional models of psychopathology such as the Research Domain of Criteria (RDoC; Cuthbert, 2014) or the Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov et al., 2017).

The continuity from normative psychological traits to psychopathology is increasingly recognized in genomic studies that find overlap not only among disorders but also between disorders and normal ranges of phenotypic variation in the population spanning cognitive (Smeland et al., 2020; Bahrami et al., 2021) and personality traits (Hindley et al., 2021, 2022), suggesting a heritable genetic liability spectrum that extends into the population (Doyle et al., 2025).

Traditionally, gene-by-environment (GxE) research has been grounded in the diathesis-stress or vulnerability-stress model, in which genetic factors are conceptualized as risk-promoting influences that, in interaction with adverse environmental contexts, may lead to the development of psychopathology (Monroe & Simons, 1991). However, the lack of specificity of risk factors—with no single exposure being necessary or sufficient for disorder onset, and the same adversity producing markedly different outcomes across individuals carrying similar genetic risk (Green et al., 2010; Uher & Zwicker, 2017; Gülöksüz et al., 2018)—seems incompatible with the model's assumption of matched vulnerabilities and matched triggers. In addition, the extensive pleiotropy both within disorders and across non-pathological traits (Hindley et al., 2022); for example, shared genetic architecture between schizophrenia, bipolar disorder, and major depressive disorder with intelligence (Smeland et al., 2020; Bahrami et al., 2021), and between schizophrenia and bipolar disorder with personality traits such as openness to experience (Lo et al., 2017) and creativity (Li et al., 2020; Kim et al., 2024); and the counterintuitive persistence of common genetic risk variants in the general population—despite their association with reduced evolutionary fitness (Belsky & Pluess, 2009; Dongen & Boomsma, 2013)—challenge this model.

In contrast, the Differential Susceptibility (DS) framework (Belsky et al., 2007; Ellis et al., 2011; Belsky & Pluess, 2013) has emerged as a compelling alternative. This perspective posits that certain genetic variants confer heightened sensitivity to environmental contexts, amplifying individuals' responsiveness to both adverse and supportive conditions—thus, yielding "for better and for worse" outcomes (Belsky et al., 2007). From this standpoint, genetic variation is not inherently pathogenic; rather, some variants function as plasticity factors that modulate the degree to which environmental inputs shape developmental trajectories.

Emerging research is offering support to the DS model in the extended psychosis phenotype employing a PGS for environmental sensitivity (PGS-ES; Keers et al., 2016). Barrantes-Vidal et al. (2025a) found that nonclinical young adults with higher PGS-ES reported elevated levels of positive schizotypy, psychotic-like experiences, depression, and anxiety under high adversity, but significantly fewer subclinical symptoms under low or no adversity. These findings were replicated and extended in a larger independent encompassing both negative and positive early experience, findings were replicated and extended to positive outcomes specifically to well-being, showing that individuals with higher PGS-ES reported greater psychopathology, poorer functioning, and lower positive mental health outcomes when

exposed to fewer positive experiences or poorer paternal parenting; but also exhibited less symptoms and more positive outcomes when exposed to supportive environments compared to individuals with lower PGS-ES (Barrantes-Vidal et al., 2025c). Importantly, similar effects were observed testing DS to context in daily-life using Experience Sampling Methodology: participants with high PGS-ES reported more paranoia and negative affect (and less positive affect) after exposure to less-positive contexts, but showed opposite effects after exposure to positive ones (Barrantes-Vidal et al., 2025b). Recently, this DS pattern of findings was replicated in the TwinssCan cohort (638 adolescent twins) on schizotypic eccentricity, functioning and social coping outcomes (Torrecilla et al., 2026). A consistent finding across these studies was that, as hypothesized, all stress-related dimensions (positive schizotypy, PLE, depression, anxiety), but not negative schizotypy, showed a DS pattern, which is consistent with evidence that the psychosocial factors are mostly critical for the positive and affective dimensions (Gibson, Alloy & Ellman, 2016; Alameda et al., 2021).

These insights, derived from a general environmental sensitivity score, raise the possibility that other PGS based on psychiatric disorder GWAS may exhibit similar patterns. This notion aligns with the Variability and Risk Model for schizophrenia (Szoke et al., 2020), which distinguishes between risk factors, which are relatively disorder-specific and directly causal, and variability factors, which are nonspecific and increase the organism's sensitivity to a wide range of inputs and promote multi-finality: the same factor, in interaction with more specific risk or opportunity (e.g., developmental enhancing) factors, may lead to pathology, to a different disorder, or to favorable outcomes. In this framework, PGS may capture both disorder-specific effects related to pathophysiology and non-specific components, which would not be deterministically pathogenic but reflect a broader transdiagnostic plasticity conditionally expressed as pernicious or adaptive as a function of the environment.

The present study

The present study aimed to extend these initial findings supporting the DS framework with a PGS of environmental sensitivity by testing, for the first time, whether disorder-related PGS also showed DS effects. Specifically, we tested the interaction between disorder-related PGS—specifically for schizophrenia (PGS-SCZ), bipolar disorder (PGS-BD), major depressive disorder (PGS-MDD), and shared schizophrenia and bipolar disorder variants (PGS-SCZ+BD)—with *both* negative and positive environmental experiences in predicting a broad range of outcomes, encompassing negative mental health (interview-ratings of schizotypy, psychotic-like experiences, and internalizing symptoms), positive mental health indicators, and functioning in the TwinssCan cohort.

It was expected that PGS-SCZ, PGS-BD, PGS-MDD, and PGS-SCZ+BD would moderate associations of both adverse and positive experiences with outcomes in a DS pattern. High-PGS individuals were expected to show higher subclinical symptoms, worse functioning, and lower well-being under adversity, and the reverse pattern under positive conditions, compared to those with lower genetic susceptibility. Furthermore, it was hypothesized that: (i) the observed DS interactions would not be limited to symptom domains traditionally linked to the specific disorder indexed by the PGS (e.g., psychotic-like experiences for PGS-SCZ) but would extend to other manifestations (e.g., internalizing symptoms, well-being), thus

supporting the notion that disorder-related PGS reflect *both* disorder-specific and broader transdiagnostic plasticity factors, and (ii) concordant PGS–phenotype interactions (e.g., PGS-SCZ predicting psychotic-like experiences, PGS-MDD predicting internalizing symptoms) would yield larger effect sizes compared to discordant interactions (e.g., PGS-MDD predicting psychotic-like experiences). Study hypotheses, methods, and data analytic procedures were preregistered at the Open Science Framework (https://osf.io/tw5sx/).

2. Methods

2.1 Participants

Data were derived from the first wave of the TwinssCan study, a general population twin cohort recruited from the prospective population-based registry East Flanders Prospective Twin Survey (EFPTS) in East Flanders, Belgium. The TwinssCan cohort included adolescents and young adults (age range at enrollment = 15–35 years) and comprised 796 twins, 43 siblings, and 363 parents assessed between April 2010 and April 2014 (Pries et al., 2017). Written informed consent was obtained from all participants. Exclusion criteria were lack of parental or caregiver consent for participants under 18 years of age and the presence of a pervasive mental disorder. The study was approved by the local ethics committee (Commissie Medische Ethiek van de Universitaire Ziekenhuizen KU Leuven, Nr. B32220107766). For the present study, we focused on the twin subsample with available genetic data. Of the 778 twins participating in the first wave, 638 provided genetic data (mean age = 17.36 years, SD = 3.60; 60.5% female). To ensure a developmentally homogeneous sample, 35 subjects (5.5% of the sample) aged 25 to 35 years were excluded, as this age group showed significative differences across most outcome dimensions. This resulted in a final analytic sample of 605 twins, 182 monozygotic twin individuals and 423 dizygotic twin individuals (mean age=16.69 years, SD = 2.24, 63% aged 15–16).

2.2 Construction of Polygenic Risk Scores

Genotypes were generated using two platforms: the Infinium CoreExome-24 and Infinium PsychArray-24 kits. Details about genotyping procedures, quality control, and imputation can be found in Supplementary Materials.

Polygenic scores were calculated based on GWAS summary statistics for schizophrenia (SCZ; Trubetskoy et al., 2022), bipolar disorder (BD; Mullins et al., 2021), shared schizophrenia and bipolar disorder liability (SCZ+BD; Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018), and major depressive disorder (MDD; Wray et al., 2018).

2.2.1. LD Clumping and P-Value Thresholding (C+T)

For the main analysis, PGSs were computed using the clumping and thresholding method implemented in PRSice-2 (Choi et al., 2020). Beta coefficients, effect alleles, and p-values were extracted from the GWAS summary statistics. Within the TwinssCan dataset (target sample), the following variants were excluded: insertions and deletions, ambiguous SNPs, SNPs with minor allele frequency (MAF) < 0.01, SNPs with imputation quality $R^2 < 0.9$, and SNPs located

in complex or long-range linkage disequilibrium (LD) regions (Price et al., 2008; see Supplementary Table 1). Only SNPs overlapping across the GWAS summary statistics (training dataset), the 1000 Genomes reference panel, and the TwinssCan dataset were retained. LD clumping was performed in two rounds using PLINK (round 1: --clump-kb 250 --clump-r2 0.5; round 2: --clump-kb 5000 --clump-r2 0.2). PGS were calculated at the following P-value thresholds: 5 x 10-6, 5 x 10-5, 5 x 10-4, 5 x 10-3, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1. After quality control, 3,366,081 variants were used in the PGS calculation. For the main analysis, the selected p-value thresholds were: SCZ PGS: $p < 0.05$, MDD PGS: $p < 0.05$. SCZ+BD shared PGS: $p < 0.05$ and BD PGS: $p < 0.10$. These thresholds were selected based on the proportion of variance explained in the respective discovery GWAS and prior literature supporting their performance.

2.3 Environmental Measures

Childhood adversity was assessed using the Childhood Trauma Questionnaire-Brief (Bernstein et al., 2003) (CTQ-B), a 28-item self-report measuring sexual, physical, and emotional abuse, as well as physical and emotional neglect before age 18. To capture experiences not covered by the CTQ-B, 13 questions adapted from the Childhood Experience of Care and Abuse interview (Bifulco et al., 1994) were included, addressing adversity in two age periods: 0–11 and 12–17 years. The total sum of endorsed experiences was added to the CTQ score, creating a comprehensive score of childhood adversity.

To assess peer-related adversity, the Retrospective Bullying Questionnaire (Schäfer et al., 2004), a self-report measure of childhood and adolescent bullying, was used. Following prior research (Rauschenberg et al., 2021), we selected two items to assess the frequency and intensity of physical, verbal, and indirect bullying in elementary school, along with five items from Part III capturing additional bullying experiences (e.g., “How many times have you skipped school or tried to avoid going to school by doing something?”). The total score reflected the overall exposure to bullying.

To measure positive childhood experiences, a four-item self-report scale (Cronbach’s $\alpha = .79$) assessing upbringing (“I had a very pleasant childhood”), parental relationships (“My parents loved each other very much”), received attention (“I received the attention I needed”), and personal privacy (“My privacy was respected”) was used.

2.4 Outcome Measures

2.4.1 Psychosis-spectrum

The Structured Interview for Schizotypy-Revised (SIS-R) is a semi-structured interview assessing 20 schizotypal traits and symptoms and 11 signs (Vollema & Ormel, 2000). In this study, 11 traits/symptoms and 4 signs were rated. Symptoms, such as magical ideation and referential thinking, were based on verbal responses, whereas signs, like goal-directed thinking and affect flatness, were behaviorally assessed. Positive (referential thinking, suspiciousness, magical ideation, illusions, psychotic symptoms and derealization/depersonalization, hypersensitivity) and negative (social isolation, introversion, restricted affect) symptom sum scores were calculated. Schizotypic signs were analyzed separately, as they capture a mixture of positive, negative and disorganized schizotypy dimensions (goal-directedness of thinking, loosening of associations, poverty of speech and eccentricity), and it is well-established that

combining different dimensions into composite scores reduces predictive power (Barrantes-Vidal & Kwapil, 2023). Additionally, the Positive subscale of the Community Assessment of Psychic Experiences (Stefanis et al., 2002) (CAPE) was used to assess the frequency of positive psychotic-like experiences (PLE) and capture the subjective evaluation of these experiences alongside the SIS-R examiner ratings.

2.4.2 Internalizing symptoms

The Symptom Checklist 90 Revised (Derogatis et al., 1976) (SCL-90-R) and the depressive subscale of the CAPE (Stefanis et al., 2002) were used to assess internalizing symptoms. From the SCL-90-R's nine dimensions, we included depression, anxiety, phobic anxiety, interpersonal sensitivity, somatization, obsessive-compulsive scales and seven additional items reflecting affective dysfunction (e.g., restless or disturbed sleep). The SCL hostility subscale was excluded, as it is conceptually more closely related with externalizing behaviors. Given strong correlations (see Supplementary Table 3) among these variables, a composite internalizing symptoms score was created to streamline analysis and minimize multiple testing. See Supplementary Methods for a detailed description of the process.

2.4.2 Functioning

Functioning was assessed using the Global Assessment of Functioning scale (Pedersen et al., 2012), a standard rating scale that assesses social, occupational, and psychological functioning. Higher scores reflect increased functioning.

2.4.3 Positive mental health outcomes

Self-esteem was measured using the Rosenberg Self-Esteem Scale (Franck et al., 2008), and well-being with the Amsterdamse Psychological Well Being scale (Ryff et al., 1995) (AWS), a 54-item self-rating inventory assessing six dimensions: environmental mastery, purpose in life, self-acceptance, autonomy, personal growth, and personal relationships. Due to strong correlations among these variables (see Supplementary Table 5), a composite score was created (see Supplementary Methods for a detailed description of the process).

General coping style was assessed using the Utrecht Coping List (Schreurs et al., 1993), which measures seven coping styles: active tackling, avoidance, comforting thoughts, expressing emotions, palliative reaction, passive reaction, and social support. To achieve a broader characterization of coping strategies and optimize the analyses, we examined its factor structure. This process yielded two distinct factors—Active and Passive Coping—whereas the Social Coping subscale was retained as a separate component. See Supplementary Methods for details.

2.5 Statistical Analysis

2.5.1 Main Analysis

Given the hierarchical structure of the data, with participants nested within twin pairs, linear mixed models were used to account for within-subject clustering of multiple observations of those who were part of the same twin pair. Analyses were conducted using version 1.4.1 of the

LEGIT package in R (Jolicoeur-Martineau et al., 2020), which is specifically designed to examine the fit of GxE interactions. Following Belsky & Widaman (Belsky & Widaman, 2018), we first used a standard regression model to check whether the interaction term yielded significant effects. Specifically, we examined whether the interaction yielded an $F > 1$, which indicates sufficient variation in the interaction term (Belsky & Widaman, 2018) to proceed to the subsequent competitive-confirmatory model testing (Widaman et al., 2012).

The competitive-confirmatory approach works by re-parameterizing the interaction model. That is, it systematically varies the parameters included in the regression equation to compare alternative GxE models. Specifically, this approach contrasts weak and strong versions of the DS, diathesis-stress, and vantage-sensitivity models and determines which provides the best fit to the data (Jolicoeur-Martineau et al., 2020). Moreover, LEGIT incorporates a recent improvement as compared to the original re-parametrization approach, by including re-parameterization of models that do not include the GxE term (intercept only, gene only, environment only, and gene and environment only) to examine the fit of these non-GxE models along with the GxE models. The best model fit is evaluated based on the lowest Akaike Information Criterion (AIC) fit index. An interaction is classified as "DS" if this model has a) the lowest AIC, and b) the 95% interval of its estimated crossover point is within observable bounds of the environmental score. However, if any of the four models without the interaction term shows the lowest AIC, the interaction will be considered as showing no evidence of GxE. Importantly, including non-GxE models in the comparison process of re-parametrized models is critical to minimize the rate of false positive findings to 5% or lower. Furthermore, the accuracy and predictive ability of the competitive-confirmatory model testing with LEGIT as compared to other methods such as the classic Regions of Significance has been documented (Jolicoeur-Martineau et al., 2020).

Associations between PGS and outcomes were examined using linear regression on standardized predictors and outcomes, yielding standardized effect sizes (β). Multiple comparisons were controlled within each PGS using false discovery rate correction (Benjamini–Hochberg). All analyses were adjusted for the first two ancestry-informative principal components (PC1 and PC2) to control for population stratification (Lin et al., 2023). Finally, resampling procedures including k-fold cross-validation and bootstrapping were conducted to assess model stability and generalizability; details are provided in the Supplementary Methods.

2.5.2. Sensitivity Analysis

To evaluate the robustness of the findings, all primary models were repeated using PGSs derived from the PGS-CS approach. Results were considered robust when the direction and statistical significance of associations were consistent across both PGS construction methods. Methodological details about sensitivity analyses, including PGS-CS derivation method can be found in Supplementary Material.

3. Results

Main effects of PGSs on outcomes are reported in Table 1 and Figure 1. PGS-MDD showed the most consistent and specific pattern of associations, being the only PGS significantly

associated with internalizing symptoms (β = 0.16, p = .001), well-being (β = −0.17, p < .000), and positive PLE (β = 0.11, p = .037 after FDR correction). A significant association was observed between PGS-SCZ and positive PLE (β = 0.09, p = .037), and between PGS-BD and active coping (β = 0.09, p = .023), though neither survived FDR correction. Similarly, PGS-SCZ+BD showed a significant association with loosening of associations (β = 0.10, p = .017), but it lost significance after FDR correction.

Gene-environment interaction (GxE) analyses are reported in Table 2 and Figures 2 and 3. For the psychosis phenotype, eccentricity was the only variable predicted by GxE models. Specifically, all PGS showed interactions with *both* childhood adverse (but not bullying) and positive experiences, except for PGS-MDD, which showed an interaction only with adverse childhood experiences. As hypothesized, competitive-confirmatory tests indicated that interactions between all PGS and adverse childhood fitted a DS model, except for PGS-MDD, which showed comparable fit for both DS and diathesis–stress models. For positive childhood experiences, only the PGS-SCZ interaction was best explained by a DS model, whereas PGS-BD and PGS-SCZ+BD showed much weaker effects (as reflected by lower F values) and fitted best a diathesis–stress model. No GxE patterns emerged for the internalizing phenotype.

Regarding positive outcomes, for wellbeing, PGS-SCZ+BD showed interaction effects with both adverse and positive childhood experiences, fitting a DS model but this effect was yielded by the low-PGS group. Similarly, for coping styles, PGS-SCZ+BD showed an interaction with primary bullying on both social and active coping, with effects carried by the low PGS group. Confirmatory analysis indicated that for social coping the best fitting model was diathesis–stress, while for active coping analysis revealed comparable fit between DS and a diathesis–stress model (Table 2; Supplementary Table 12).

Finally, functioning emerged as a significant outcome of the interaction between all PGS and all three environmental variables, fitting a DS model in all cases carried by high PGS scorers. F values were highest for PGS-SCZ, followed by PGS-SCZ+BD, PGS-BD, and PGS-MDD.

Results from the primary PGS construction method (C+T) were broadly replicated using PRS-CS-auto, supporting the robustness of the main findings (see Supplementary Material).

4. Discussion

To our knowledge, this is the first study testing the DS hypothesis using psychosis and affective disorders spectrum PGSs in interaction with *both* adverse and positive experiences in childhood to predict a broad variety of positive and negative outcomes—including interview-ratings of schizotypy traits, signs, and symptoms as well as functioning. No previous work has explored whether differential susceptibility to the environment could be detected within the variability of disorder-related PGS, and less so in relation to the extended psychosis phenotype—except for our work with a PGS specifically focused on Environmental Sensitivity (PGS-ES) (Barrantes-Vidal et al., 2025a,b; Torrecilla et al., 2026).

Results showed that adolescents with higher disorder-related PGSs showed higher levels of dysfunction and eccentricity when exposed to early adverse family and school contexts but,

at the same time, they presented better adjustment when exposed to low adversity or high positive experiences as compared to adolescents with low genetic 'liability', thus consistent with the hypothesized DS pattern. This means that polygenic scores indexing *risk* to disorders indeed predict *risk* for subclinical psychosis expression and malfunctioning *in the context* of an unfavorable childhood yet, the same 'risk' scores, do also predict lower symptom expression and better functioning *in the context* of favorable childhood upbringing. Importantly, a diathesis-stress approach focused only on the risk-amplifying effects of adversity would have captured only one side of these interactions, overlooking the adaptive advantage shown by high-PGS adolescents under supportive environmental conditions. These findings are consistent with the evolutionary grounded notion that some "vulnerability" genes, found in relatively high frequencies across populations, might be better conceptualized as "plasticity" genes, as they increase susceptibility to both adverse and supportive contexts and yield disparate outcomes in terms of poor to superior health and adaptation, respectively (Belsky et al., 2009; Van Dongen & Boomsma, 2013; Szoke et al., 2020).

DS effects emerged across all environmental exposures for general functioning, whereas for schizotypic eccentricity they were more circumscribed to the interactions between the PGSs with adverse family environment. As hypothesized, results support a transdiagnostic PGS continuum across disorders, as 1) DS patterns were consistent for all PGSs examined, including PGS-MDD, consistent the hypothesis of an affective pathway to psychosis (van Os et al. 2022; Alameda et al., 2024), 2) while showing graded effect sizes with the strongest associations observed for SCZ (or SCZ+BD), followed by BD and MDD supporting a genetic continuum of severity (Smigielski et al., 2021; Allardice et al., 2018). Overall, these findings converge with earlier DS evidence using a PGS for environmental sensitivity in non-clinical youth (Barrantes-Vidal et al., 2025a,b,c; Torrecilla et al., 2026) and extend this evidence to disorder-based PGSs, suggesting that the common variant polygenic architecture of psychiatric disorders may also encompass a broader pleiotropic component partly reflecting genetic variability in susceptibility to the environment.

The convergence of GxE effects on eccentricity and functioning aligns with the adolescent non-clinical composition of the sample ($M_{age} \approx 17$; 60% 15-16 years old). At this developmental stage, individuals are likely in a pluripotent phase of liability (Hartmann et al., 2021) and plasticity, in which psychopathology tends to be undifferentiated and subthreshold, with broad dysregulation preceding the emergence of specific syndromes (McGorry et al., 2024). It is therefore consistent that effects emerged for these two observer-rated, integrative outcomes: eccentricity, a core schizotypy sign capturing oddities in speech, behavior, and social presentation, indexing the behavioral and social manifestation of a blend of positive and especially disorganized schizotypy traits and cognitive-behavioral disruptions (Kemp et al., 2022); and functioning, an index of social role and psychological adjustment, which reflects impairment across multiple domains without directly tapping specific symptoms. Notably, functioning was assessed using the GAF, a bipolar measure ranging from superior functioning (rather than mere absence of symptoms) to severe impairment, making it well suited to capture differential susceptibility effects. Their relevance as early detection markers is further underscored by evidence that eccentric behavior and a gradual decline in social and role

functioning are among the strongest early predictors of later prodromal and psychotic outcomes (Welham et al., 2008; Lv et al., 2015).

DS effects for functioning were consistent across PGS and environments, whereas those for eccentricity were more circumscribed. Specifically, while effects for adverse childhood were robust across PGS, effects for positive childhood were relatively strong for PGS-SCZ, weaker for BD and SCZ+BD (with evidence of model instability in bootstrap analyses), and absent for MDD. This might partly reflect the quite narrow scope of the positive childhood measure, capturing supportive and nurturing family environments, in contrast to the broad range of and number of experiences covered by the adversity factor. Accordingly, effects are retained primarily for the PGS most strongly implicated in the eccentricity phenotype, consistent with the greater prominence of cognitive and disorganization-related impairments in schizophrenia relative to MDD and BD (McCutcheon et al., 2023; Ohi et al., 2023; Trotta et al., 2015).

Furthermore, low scores on the positive childhood measure, capturing absence of warmth, attention, and nurturing, are conceptually proximal to emotional neglect (Bernstein et al., 2003), which has been shown to be specifically associated with the negative and depressive dimensions (Alameda et al., 2021; Sheinbaum et al., 2024), for which we lack a comparable broad, observer-rated proxy. Internalizing symptoms were measured with items from the SCL-90-R, which presented very low endorsement, probably due to the measure's focus on severe symptomatology (e.g., thinking about death or dying, being afraid to leave the house alone) and clinical manifestations (Derogatis et al., 1996).

Surprisingly, we did not find significant interactions between PGSs and bullying for eccentricity, given that bullying has been consistently linked to psychosis risk. This may be explained by the age distribution of the sample (70% aged 15–16), which limited assessment to primary school bullying (ages 6–12), making it the only environmental exposure that did not capture very early childhood experiences. At this developmental stage, the longer-term psychological consequences of earlier or ongoing bullying may not yet have crystallized into more specific expressions such as eccentric behavior, and may instead be detectable only at the broader level of psychosocial functioning, consistent with longitudinal research indicating that the adverse psychological effects of childhood bullying often unfold gradually across late adolescence and young adulthood (Trotta et al., 2013; Arseneault, 2018).

Regarding positive outcomes, effects on well-being and active coping were confined to individuals with lower PGS SCZ+BD scores. Low-liability individuals showed a DS pattern for well-being—that is, reporting higher well-being under positive experiences and lower well-being under adversity—and a diathesis-stress pattern for active coping, with lower coping abilities when exposed to bullying. These attenuated effects may partly reflect limitations of the well-being measure: the Ryff Psychological Well-Being Scale captures eudaimonic dimensions—autonomy, purpose in life, personal growth, self-acceptance—that presuppose identity consolidation and goal directedness that are developmentally incomplete in mid-adolescence (Ryff et al., 1995), likely limiting variance and environmental sensitivity in this age group, consistent with prior null findings for this measure in interaction with PGS of environmental sensitivity in the same sample (Torrecilla et al., 2026). Beyond measurement constraints, the uniformly lower well-being profile of high-liability individuals may reflect

subtle negative-symptom-like features (e.g., reduced goal-directed behavior, avolition, social withdrawal) associated with subclinical psychosis-spectrum liability, constraining agency-dependent dimensions of well-being such as environmental mastery and purpose in life independently of environmental quality. This interpretation might be consistent with the notion that the SCZ+BD PGS, capturing a broad psychosis liability index with a strong affective component, is associated with greater clinical severity, including higher levels of psychotic symptoms, earlier age of onset, and increased likelihood of hospitalization (PGC BD–SCZ Working Group, 2018).

Overall, effects and variance explained were consistently stronger for PGS-SCZ (or PGS-SCZ+BD), consistent with the notion that schizophrenia indexes the severe end of a general psychopathology spectrum (Claridge, 1997; van Os & Reininghaus, 2016) and could be considered a transdiagnostic severity marker (Marsman et al., 2020; Pries et al., 2020). PGS-SCZ captures a larger aggregate of GWAS-significant loci, with a substantial proportion indexing shared liability rather than schizophrenia-specific risk alone (Andreassen et al., 2023; Owen et al., 2025). This likely also reflects the superior power-of PGS-SCZ, as schizophrenia has higher SNP-based heritability (i.e., a greater proportion of phenotypic variance attributable to common genetic variants), providing a stronger signal for GWAS to detect, alongside a more homogeneous and better-defined phenotype compared to BD and MDD (Owen et al., 2025).

Although G×E effects were largely transdiagnostic, regression analyses (Table 1; Figure 1) suggest some specificity between PGSs and outcomes. PGS-MDD was the only score significantly associated with depression, internalizing symptoms, well-being, and non-confrontative/passive coping (the latter not surviving FDR correction), highlighting a specific contribution of depression-related genetic liability to symptom profiles characterized by reduced positive affect and inwardly directed distress. In addition, though not surviving FDR correction, unique associations emerged between PGS-BD and active coping and between PGS-SCZ and PGS-SCZ+BD with attentional focus and loosening of associations, respectively. The association between PGS-BD and active coping—a self-report measure reflecting a confrontative, optimistic style and high perceived self-efficacy—may reflect a tendency to score higher on such traits related to hypomanic personality traits and states, which can promote a "hyper-positive" self-view and overestimation of coping resources (Lee et al., 2010), while associations for PGS-SCZ and PGS-SCZ+BD are conceptually consistent with the stronger link between SCZ-related variants and cognitive disorganization (Murray et al., 2017; Ohi et al., 2023). While these effects were modest and did not survive FDR correction, they suggest that PGSs retain some specificity in predicting symptom-level outcomes.

Zhang and Belsky (2022) argued that disorder-based PGSs are not well suited to test DS because they are derived from GWAS identifying variants associated with the phenotype (i.e., a psychiatric disorder) irrespective of environmental context, thus embedding an unconditional genetic effect that biases G×E analyses toward diathesis–stress interpretations. In contrast, polygenic plasticity scores (e.g., PGS-ES) are explicitly designed to capture environmentally contingent genetic effects (i.e., G×E loci). Consistent with this, main effects were more concordant with disorder-specific symptomatology. However, although disorder-PGSs primarily reflect marginal effects averaged across heterogeneous environments—thereby

attenuating environmentally contingent signals—these can still be recovered when explicitly modeled through interaction terms (Penner-Goeke & Binder, 2026). Indeed, G×E effects emerged for broader, transdiagnostic outcomes and did not overlap with main effects. Importantly, the competitive-confirmatory framework implemented in LEGIT directly addresses this issue by distinguishing significant findings driven by main genetic effects from those better explained by G×E models, selecting DS only when it provides superior fit to simpler models. Accordingly, several outcomes with significant main effects were classified as non-G×E, as their genetic signal was better captured without interaction terms (Supplementary Tables 10-13). Together, these findings suggest that disorder-PGSs may index two partially distinct components: a disorder-specific liability reflected in main effects, and a plasticity component whose effects are environmentally contingent and that becomes evident only under explicit G×E modeling.

A limitation of this study is that generalizability of findings is restricted to non-clinical White adolescents. Although this population represents a key demographic at the intersection of developmental vulnerability and heightened sensitivity to sociocultural influences (Blakemore & Mills, 2014), future research should examine whether DS patterns extend to other ethnicities and populations, including at-risk or clinically diagnosed groups. Longitudinal studies are also needed to clarify how genetic liability and DS patterns evolve across developmental stages. In addition, future studies could benefit from broadening environmental assessment including frameworks such as the exposome (Gülöksüz et al., 2018), covering a wide variety of exposures across the lifespan.

Our findings support a paradigm shift in how genetic risk and vulnerability are conceptualized. Rather than deterministically encoding pathology, disorder-related PGS may index a heterogeneous set of genetic variants with distinct effects: some operating in a diathesis–stress manner, while others may function as non-specific plasticity factors that amplify responsiveness to environmental exposures in both directions. Empirical support for this notion comes from recent genomic work identifying two biologically distinct subsets of pleiotropic loci shared between schizophrenia, educational attainment and cognitive performance: concordant loci—where higher schizophrenia liability is associated with lower cognitive performance and educational attainment, which map onto prenatal neurodevelopmental processes, and discordant loci—where higher schizophrenia liability is paradoxically linked to higher cognitive performance and educational attainment, which map onto postnatal brain functions such as synaptic signaling (Bhattacharyya et al., 2025). This bifurcation suggests that PGSs may aggregate variants indexing distinct biological pathways with different developmental timing, with some contributing to vulnerability—for instance, through early neurodevelopmental processes—while others may not exert a deterministic risk effect and can also be involved in favorable outcomes. The pleiotropic pattern of the latter fits with the variability model (Szöke et al., 2020), which posits that certain risk-related variants do not uniformly elevate liability but instead broaden phenotypic variability, thus amplifying both maladaptive and highly adaptive expression. From this perspective, part of what is captured by disorder-related PGSs may be a generalized capacity for heightened plasticity, helping to reconcile the persistence of disorder-associated common alleles despite their apparent fitness costs.

These findings carry important clinical implications, reinforcing the need to move beyond rigid categorical models toward a transdiagnostic framework that prioritizes early identification of behavioral and functional indicators through which genetic liability manifests before the emergence of fully developed psychiatric syndromes. Global functioning and eccentricity, as illustrated by the present study and previous findings (Barrantes-Vidal et al., 2025a,b,c; Torrecilla et al., 2026), may serve as useful proxies for early detection. Critically, if genomic liability partly reflects environmental sensitivity, then the same plasticity factors that increase vulnerability under adversity also enhance responsiveness to protective influences—meaning that supportive environments may buffer risk and promote adaptive functioning *especially* among genetically susceptible individuals.

This shifts the clinical focus from risk stratification alone toward early, proportional interventions that target shared risk factors and non-specific symptoms while fostering resilience, adaptive coping (McGorry & Mei, 2018; Shah et al., 2020), and the potential positive expressions associated with heightened genetic liability/susceptibility (Claridge, 1997; Claridge & Barrantes-Vidal, 2013). This is particularly important given evidence that interventions which categorize individuals into rigid diagnostic silos risk stigma, overdiagnosis, and iatrogenic harm—especially when narrowly focused on risk reduction in adolescent populations (Bastounis et al., 2017; Foulkes & Stringaris, 2023)—making resilience-focused, transdiagnostic prevention an urgent priority in the context of the current youth mental health crisis (McGorry, 2024).

Future multi-trait GWAS and pleiotropic meta-analytic approaches that jointly model disorder-related and non-pathological phenotypes will be essential for disentangling these partially overlapping pathways, clarifying how the same common-variant architecture can simultaneously underlie both vulnerability and adaptive outcomes and its context dependent expression. Failing to account for this plasticity risks misinterpreting the meaning of genetic associations, obscuring the dynamic continuum between pathology and adaptive variation, and foreclosing avenues for personalized, resilience-focused intervention.

Supplementary materials available at: **https://osf.io/8k7ws/**

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Tables and Figures

Table 1. Standardized Associations between Polygenic Scores and Mental Health Outcomes

Outcome	PGS	*β*	SE	P value	pFDR
SIS-R Positive Symptoms	PGS-SCZ	0.07	0.04	.110	.330
	PGS-BD	0.07	0.04	.076	.331
	PGS-SCZ+BD	0.06	0.04	.144	.424
	PGS-MDD	0.09	0.04	**.027**	.087
SIS-R Negative Symptoms	PGS-SCZ	−0.05	0.04	.203	.330
	PGS-BD	−0.06	0.04	.156	.367
	PGS-SCZ+BD	−0.04	0.04	.290	.539
	PGS-MDD	0.05	0.04	.208	.387
Positive PLE (CAPE)	PGS-SCZ	0.09†	0.04	**.037**	.241
	PGS-BD	0.00	0.04	.934	.949
	PGS-SCZ+BD	0.02	0.04	.700	.909
	PGS-MDD	0.11*	0.04	**.008**	**.037**
Focus of Attention	PGS-SCZ	0.10†	0.04	**.015**	.202
	PGS-BD	0.04	0.04	.287	.533
	PGS-SCZ+BD	0.07	0.04	.086	.407
	PGS-MDD	0.03	0.04	.519	.674
Loosening of Associations	PGS-SCZ	0.05	0.04	.213	.330
	PGS-BD	0.06	0.04	.132	.367
	PGS-SCZ+BD	0.10†	0.04	**.017**	.222
	PGS-MDD	−0.02	0.04	.715	.845
Eccentricity	PGS-SCZ	0.03	0.04	.558	.558
	PGS-BD	0.04	0.04	.328	.534
	PGS-SCZ+BD	0.05	0.04	.237	.514
	PGS-MDD	0.04	0.04	.394	.569
Poverty of Speech	PGS-SCZ	0.03	0.04	.513	.555
	PGS-BD	0.03	0.04	.422	.609
	PGS-SCZ+BD	0.03	0.04	.491	.709
	PGS-MDD	0.00	0.04	.928	.928
Internalizing Factor	PGS-SCZ	0.05	0.04	.276	.330
	PGS-BD	0.02	0.04	.573	.745

Outcome	PGS	*β*	SE	P value	pFDR
	PGS-SCZ+BD	0.01	0.04	.839	.909
	PGS-MDD	0.16**	0.04	**.000**	**.001**
Well-being	PGS-SCZ	−0.05	0.04	.229	.330
	PGS-BD	0.00	0.04	.949	.949
	PGS-SCZ+BD	−0.01	0.04	.798	.909
	PGS-MDD	−0.17***	0.04	**.000**	**.000**
Social Coping	*PGS-SCZ*	0.07	0.04	.080	.330
	PGS-BD	0.08	0.04	.058	.331
	PGS-SCZ+BD	0.06	0.04	.163	.424
	PGS-MDD	0.00	0.04	.916	.928
Active Coping	PGS-SCZ	0.06	0.04	.169	.330
	PGS-BD	0.09†	0.04	**.023**	.298
	PGS-SCZ+BD	0.07	0.04	.094	.407
	PGS-MDD	−0.06	0.04	.128	.277
Passive Coping	PGS-SCZ	0.05	0.04	.279	.330
	PGS-BD	0.06	0.04	.169	.367
	PGS-SCZ+BD	0.03	0.04	.486	.709
	PGS-MDD	0.08	0.04	**.056**	.145
Functioning	PGS-SCZ	−0.05	0.04	.242	.330
	PGS-BD	0.00	0.04	.934	.949
	PGS-SCZ+BD	0.00	0.04	.987	.987
	PGS-MDD	−0.04	0.04	.303	.492

Note. All models adjusted for ancestry principal components (PC1, PC2).
† p < .05 (uncorrected). * pFDR < .05. ** pFDR < .01. *** pFDR < .001.
β = standardized regression coefficient; SE = standard error; pFDR = p-value after Benjamini–Hochberg false discovery rate correction. PGS-SCZ: Polygenic Score for Schizophrenia;
PGS-SCZBD: Polygenic Score for shared liability for Schizophrenia and Bipolar Disorder;
PGS-BD: Polygenic Score for Bipolar Disorder; PGS-MDD: Polygenic Score for Major Depression Disorder.

Table 2. Regression models of Gene-Environment interactions between Disorder-related Polygenic Scores and Childhood Adverse, Positive, and Bullying Experiences on Transdiagnostic Outcomes: Main Effects and Best-Fitting Interaction Models

	PGS x Childhood Adversity			PGS x Positive Childhood			PGS x Primary Bullying		
	Est. (S.E.)	F ratio	Best GxE model fit[b]	Est. (S.E.)	F ratio	Best GxE model fit[b]	Est. (S.E.)[a]	F ratio	Best GxE model fit[b]
Psychosis spectrum									
CAPE Positive PLE									
PGS-SCZ (p < .05)	−0.008(.015)	0.30	-	−0.006(.008)	0.53	-	0.003(.009)	0.09	-
PGS-BD (p < .10)	−0.012(.014)	0.67	-	−0.005(.008)	0.44	-	**−0.013(.008)**$^{+}$	**2.75**	E only
PGS-SCZ+BD (p < .05)	−0.022(.069)	0.10	-	**−0.080(.040)***	**4.04**	E only	−0.014(.043)	0.11	-
PGS-MDD (p < .50)	−0.022(.043)	0.26	-	−0.018(.018)	0.92	-	−0.016(.020)	0.68	-
SIS-R Interview-based									
Positive Dimension									
PGS-SCZ (p < .05)	**0.026(.019)**	**1.86**	E only	**−0.015(.011)**	**2.15**	GE only	−0.001(.011)	0.01	-
PGS-BD (p < .10)	**−0.020(.018)**	**1.12**	GE only	0.006(.010)	0.36	-	−0.005(.010)	0.22	-
PGS-SCZ+BD (p < .05)	0.086(.088)	0.95	-	**−0.079(.051)**	**2.39**	GE only	−0.032(.054)	0.34	-
PGS-MDD (p < .50)	0.042(.057)	0.54	-	0.002(.025)	0.00	-	0.012(.025)	0.21	-
Negative Dimension									
PGS-SCZ (p < .05)	**0.044(.026)***	**3.00**	GE only	**−0.017(.014)**	**1.63**	E only	0.011(.015)	0.51	-
PGS-BD (p < .10)	−0.013(.025)	0.30	-	**0.017(.013)**	**1.85**	E only	**−0.015(.014)**	**1.11**	E only
PGS-SCZ+BD (p < .05)	0.038(.118)	0.11	-	−0.011(.066)	0.03	-	**−0.078(.073)**	**1.13**	E only
PGS-MDD (p < .50)	0.057(.076)	0.56	-	0.003(.032)	0.01	-	−0.030(.034)	0.77	-
SIS-R Observation-based									
Eccentricity									
PGS-SCZ (p < .05)	**0.031(.010)****	**8.85**	DS w	**−0.017(.005)****	**9.94**	DS w	0.006(.006)	0.91	-
PGS-BD (p < .10)	**0.025(.010)***	**6.30**	DS w	**−0.006(.005)**	**1.44**	Diathesis w	**0.007(.006)**	**1.45**	E only
PGS-SCZ+BD (p < .05)	**0.151(.047)****	**10.31**	DS w	**−0.042(.026)**	**2.54**	Diathesis w	**0.042(.029)**	**2.10**	GE only
PGS-MDD (p < .50)	**0.037(.031)**	**1.44**	DS s	−0.003(.013)	0.07	-	−0.009(.013)	0.46	-
Loosening of associations									
PGS-SCZ (p < .05)	0.000(.004)	0.00	-	0.001(.002)	0.31	-	−0.001(.003)	0.04	-
PGS-BD (p < .10)	−0.002(.004)	0.35	-	0.001(.002)	0.42	-	0.001(.002)	0.13	-
PGS-SCZ+BD (p < .05)	0.006(.019)	0.11	-	0.001(.011)	0.02	-	−0.006(.012)	0.27	-
PGS-MDD (p < .50)	**−0.019(.012)**	**2.40**	Intercept only	0.004(.005)	0.71	-	0.002(.006)	0.15	-
Focus of attention									

PGS-SCZ (p < .05)	**0.024(.008)****	**8.31**	G only	**−0.012(.004)****	**7.21**	G only	**0.006(.005)**	**1.57**	G only
PGS-BD (p < .10)	−0.000(.008)	0.00	-	0.004(.004)	0.86	-	−0.001(.004)	0.01	-
PGS-SCZ+BD (p < .05)	**0.086(.038)***	**5.21**	G only	−0.014(.021)	0.41	-	0.012(.024)	0.24	-
PGS-MDD (p < .50)	0.001(.025)	0.00	-	−0.004(.010)	0.13	-	0.003(.011)	0.07	-
Poverty of speech									
PGS-SCZ (p < .05)	**−0.010(.009)**	**1.20**	Intercept only	0.003(.005)	0.38	-	**−0.006(.005)**	**1.10**	Intercept only
PGS-BD (p < .10)	**−0.010(.009)**	**1.44**	Intercept only	0.003(.004)	0.43	-	−0.003(.005)	0.41	-
PGS-SCZ+BD (p < .05)	−0.039(.041)	0.89	-	0.022(.023)	0.89	-	**−0.029(.026)**	**1.28**	Intercept only
PGS-MDD (p < .50)	−0.023(.027)	0.75	-	0.008(.011)	0.54	-	**−0.015(.012)**	**1.64**	Intercept only
Internalizing factor									
PGS-SCZ (p < .05)	**0.068(.050)**	**1.84**	E only	**−0.050(.027)**+	**3.53**	E only	**0.075(.030)***	**6.14**	E only
PGS-BD (p < .10)	−0.040(.048)	0.69	-	0.013(.026)	0.26	-	0.008(.028)	0.08	-
PGS-SCZ+BD (p < .05)	0.209(.229)	0.83	-	**−0.290(.132)***	**4.85**	E only	**0.253(.146)**+	**3.02**	E only
PGS-MDD (p < .50)	**0.293(.143)***	**4.22**	GE only	**−0.121(.060)***	**4.03**	GE only	**0.072(.067)**	**1.17**	GE only
POSITIVE									
Well-being									
PGS-SCZ (p < .05)	**0.098(.046)***	**4.59**	DS w / E only	**−0.042(.022)**+	**3.54**	E only	**−0.051(.028)**+	**3.23**	E only
PGS-BD (p < .10)	**0.085(.044)***	**3.83**	E only / DS w	**−0.041(.021)**+	**3.68**	E only	0.019(.026)	0.56	-
PGS-SCZ+BD (p < .05)	**0.580(.208)****	**7.74**	DS w	**−0.216(.111)**+	**3.79**	DS w	−0.090(.137)	0.43	-
PGS-MDD (p < .50)	0.080(.131)	0.38	-	0.042(.051)	0.68	-	−0.057(.063)	0.83	-
Coping Styles									
Active Coping									
PGS-SCZ (p < .05)	−0.004(.052)	0.01	-	0.014(.026)	0.27	-	**0.036(.030)**	**1.41**	GE only
PGS-BD (p < .10)	0.030(.049)	0.38	-	**−0.042(.025)**+	**2.84**	GE only	**0.040(.027)**	**2.13**	GE only
PGS-SCZ+BD (p < .05)	0.021(.235)	0.01	-	−0.017(.128)	0.02	-	**0.347(.145)***	**5.71**	DS w / Diath w
PGS-MDD (p < .50)	0.102(.148)	0.48	-	−0.004(.060)	0.00	-	**0.073(.068)**	**1.17**	E only
Passive Coping									
PGS-SCZ (p < .05)	**−0.099(.052)***	**3.67**	E only	−0.004(.026)	0.02	-	**0.041(.031)**	**1.83**	E only
PGS-BD (p < .10)	**−0.068(.050)**	**1.87**	E only	0.021(.025)	0.67	-	−0.009(.028)	0.11	-
PGS-SCZ+BD (p < .05)	**−0.482(.237)***	**4.13**	E only	0.054(.130)	0.17	-	0.116(.147)	0.62	-
PGS-MDD (p < .50)	**0.272(.149)**+	**3.35**	GE only	−0.045(.060)	0.55	-	**0.133(.068)***	**3.88**	E only
Social Coping									
PGS-SCZ (p < .05)	**−0.268(.211)**	**1.62**	GE only	0.028(.107)	0.07	-	−0.028(.125)	0.05	-
PGS-BD (p < .10)	0.107(.202)	0.28	-	−0.007(.103)	0.00	-	**0.257(.113)***	**5.18**	GE only
PGS-SCZ+BD (p < .05)	−0.870(.970)	0.80	-	0.075(.529)	0.02	-	**1.213(.600)***	**4.09**	DS w / Diath w

PGS-MDD (p < .50)	−0.224(.611)	0.13	-	**0.264(.245)**	**1.16**	E only	**0.398(.277)**	**2.06**	E only
Functioning									
PGS-SCZ (p < .05)	**−1.606(.323)*****	**24.66**	DS w	**0.718(.168)*****	**18.29**	DS w	**−0.793(.189)*****	**17.68**	DS w
PGS-BD (p < .10)	**−0.880(.308)****	**8.17**	DS w	**0.372(.160)***	**5.39**	DS w	**−0.318(.171)**$^{+}$	**3.45**	DS w
PGS-SCZ+BD (p < .05)	**−7.494(1.464)*****	**26.21**	DS w	**3.254(.829)*****	**15.40**	DS w	**−2.774(.917)****	**9.15**	DS w
PGS-MDD (p < .50)	**−1.365(.933)**	**2.14**	DS w	**0.466(.392)**	**1.41**	Diath w / DS w	**−0.689(.428)**	**2.59**	DS w

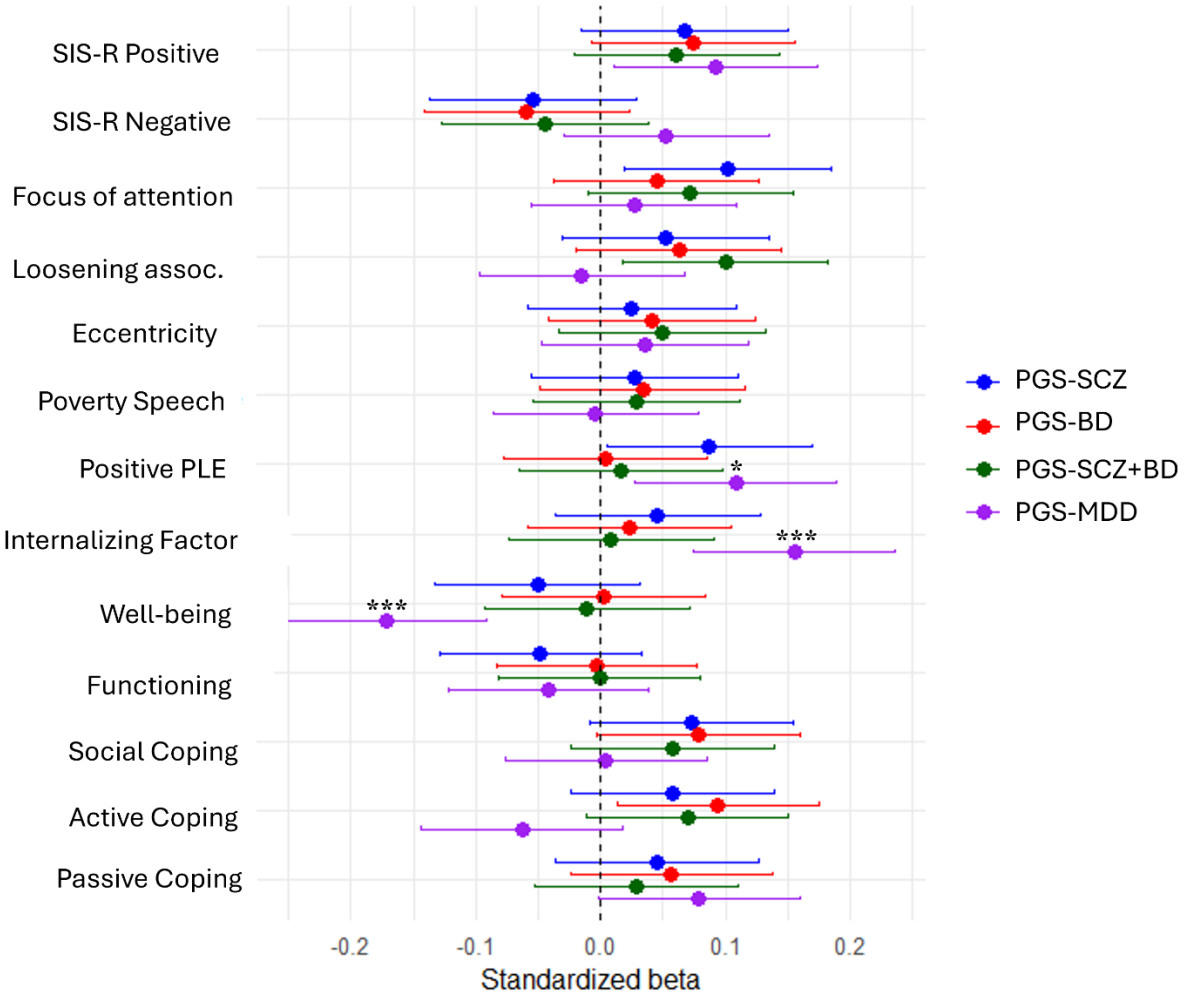
[a] Adjusted for ancestry PC1 and PC2.

[b]Model selection was based on Akaike Information Criterion (AIC), with lower values indicating better fit. Full model comparison results including AIC values for all competing models are reported in Supplementary Tables S5–S8.

Notes. The table presents main effects of each PGS and environmental exposure, and the best-fitting GxE interaction model as identified through competitive-confirmatory analysis using the LEGIT R package. Interactions with $F > 1$ are **bolded**.* $p<.05$, ** $p<.01$, *** $p<.001$, $^{+}$ $p<.10$.

Est: Estimate, S.E: Standard Error; PGS-SCZ: Polygenic Score for Schizophrenia; PGS-SCZBD: Polygenic Score for shared liability for Schizophrenia and Bipolar Disorder; PGS-BD: Polygenic Score for Bipolar Disorder; PGS-MDD: Polygenic Score for Major Depression Disorder; DS w: Differential Susceptibility weak; Diath w: Diathesis-stress weak; G only: main effect of the genetic score only; E only: main effect of the environmental score only; GE only: main effects of genetic and environmental scores only.

Figure 1. Forest Plot of Standardized Associations between Disorder-related Polygenic Scores and Mental Health Outcomes



All models adjusted for ancestry principal components (PC1, PC2). p-values are Benjamini–Hochberg FDR-corrected. β = standardized regression coefficient. Error bars represent 95% confidence intervals. † p < .05 (uncorrected). * pFDR < .05. ** pFDR < .01. *** pFDR < .001. PGS-SCZ: Polygenic Score for Schizophrenia; PGS-SCZBD: Polygenic Score for shared liability for Schizophrenia and Bipolar Disorder; PGS-BD: Polygenic Score for Bipolar Disorder; PGS-MDD: Polygenic Score for Major Depression Disorder.

Figure 2. Interactions between PGSs and Childhood Adversity on Eccentricity fitting a Differential Susceptibility model.

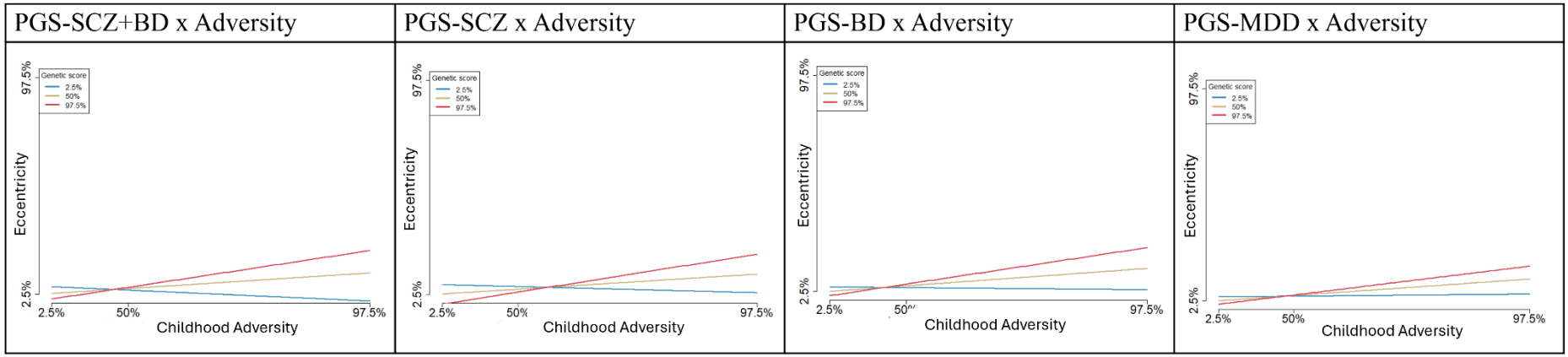
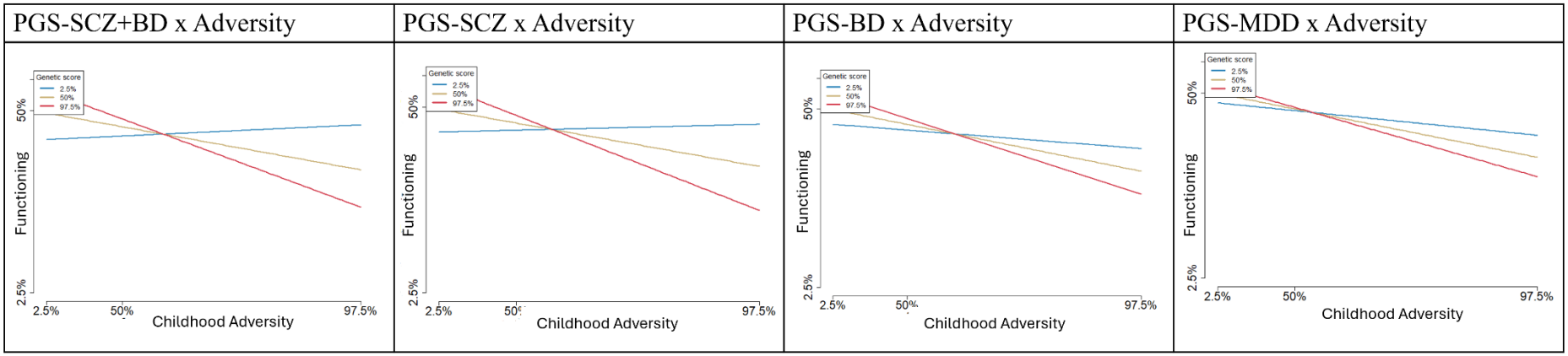


Figure 3. Interactions between PGSs and Adverse Childhood on Functioning fitting a Differential Susceptibility model.



[a] Functioning emerged as a significant outcome of the interaction between all PGS and the three environmental variables. For brevity, only plots for adverse experiences are shown, as similar patterns were observed for positive experiences and bullying.

SECTION 3

TOWARDS THE ECOLOGICAL ASSESSMENT OF ENVIRONMENTAL SENSITIVITY IN DAILY LIFE

Chapter 6

Assessment of Environmental Sensitivity in Real-life Contexts with Experience Sampling Methodology: Item Development and Results of Focus Groups with Clinical and Non-clinical Participants

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Submitted

Abstract

Individuals differ in their levels of sensitivity towards environmental influences—both positive and negative—due to individual variations in the perception and processing of internal and external experiences. Although the retrospective assessment of sensitivity has advanced, ecological approaches are needed to capture how sensitivity is expressed in daily life and understand its interaction with internal and contextual factors. This study developed and qualitatively evaluated a set of Experience Sampling Methodology items to assess momentary sensitivity to context, reactivity and social context in daily life.

A pool of items was developed based on contemporary sensitivity theory. Their suitability was evaluated through four focus groups using cognitive interviewing techniques. The groups included both non-clinical and clinical participants at elevated risk for, or with, a psychotic disorder. Feedback from the focus groups informed item refinement, resulting in a set of clear items assessing momentary sensitivity to context.

This study provides a novel, qualitatively validated tool for assessing sensitivity in daily life across non-clinical and clinical populations. The measure enables investigation of sensitivity as a dynamic, context-dependent construct, with implications for personalized assessment and for understanding how sensitivity shapes risk, resilience, and mental health outcomes "for better and for worse" within person–context interactions.

1. Introduction

Individuals differ significantly in their susceptibility (or sensitivity) to negative and positive environmental influences (Belsky & Pluess, 2009, 2013; Pluess, 2015; Pluess & Belsky, 2013). These differences stem partly from variations in how individuals perceive and process information about internal and external experiences—a concept known as sensory processing sensitivity (SPS; Aron & Aron, 1997), with higher levels of this trait involving sensitivity to subtle stimuli, susceptibility to overstimulation, deeper cognitive processing, and heightened emotional reactivity (Aron et al., 2012; Greven et al., 2019). More recently, SPS has been integrated into the broader framework of environmental sensitivity (Pluess, 2015). The Diathesis-Stress or Vulnerability-Stress model has traditionally assumed that individuals with higher sensitivity to the environment are more vulnerable to adverse conditions and likely to show poor outcomes (Monroe & Simons, 1991). In contrast, the theory of Differential Susceptibility to the Environment (DS; Belsky, Bakermans-Kranenburg & Van IJzendoorn, 2007; Ellis et al., 2011; Belsky & Pluess, 2013) extended this model by posing that such individuals are not only more susceptible to negative influences but also more sensitive to positive experiences, and therefore better able to benefit from supportive environments. DS suggests that heightened sensitivity functions as a 'plasticity factor,' with individuals varying along a continuum of greater or lesser plasticity to both positive and negative environmental inputs (Belsky et al., 2009; Ellis et al., 2011). This entails that heightened sensitivity could increase the risk of poor or psychopathological outcomes under negative environmental influences but also act as a developmental enhancing factor under positive ones (Van Ijzendoorn & Bakermans-Kranenburg, 2015). This is particularly relevant for individuals considered at risk for mental health disorders, as it highlights their potential to benefit from supportive relationships, enriching environments, and therapeutic interventions—rather than focusing solely on their vulnerability to psychosocial stressors (Thakkar et al., 2023).

SPS has traditionally been assessed using self-report measures, with the Highly Sensitive Person (HSP; Aron & Aron, 1997) scale and its short version (Pluess et al., 2023) being the most widely used. Although these measures have reliable assessed individual differences in sensitivity (Lionetti et al., 2018), the evolving conceptualization of the trait over the years has underscored the need for their revision (Greven et al., 2019). In response to these advancements, the newly developed Highly Sensitive Person Scale-Revised (HSP-R; Pluess et al., 2024) places greater emphasis on the positive aspects of sensitivity and incorporates newly recognized core traits, such as sensitivity to positive experiences and social cues. Furthermore, alternative scales, like the Sensory Processing Sensitivity Questionnaire (SPSQ; De Gucht et al., 2022) and the DOES scale (Gubler et al., 2024), have emerged to emphasize the positive dimensions of sensitivity. Recently, the assessment of SPS has evolved to incorporate observational (HSC Rating-System; Lionetti et al., 2019) and interview-based (Highly Sensitive Child – Interview, HSC-I; Kähkönen et al., 2024) methods, although these measures have so far been limited to children. The emergence of these new instruments highlights the growing interest in understanding and measuring sensitivity from the perspective of individual differences.

Despite these notable advances in retrospective, trait-level assessment, environmental sensitivity is inherently highly context-dependent; therefore, it is expected that the expression of this trait also varies as a responsive, state-dependent quality shaped by a broad range of factors, such as internal emotional and cognitive states as well as external features of the environment. This expanded perspective aligns with the integrative framework described by Pluess (2015), which positions SPS within the broader domain of environmental sensitivity and adds two critical distinctions that elucidate the construct's multidimensional nature. Firstly, sensitivity should be differentiated from responsivity. Sensitivity refers to the depth of perceptual and cognitive processing of external stimuli (the input), whereas responsivity refers to the observable behavioural output resulting from that processing. Whereas sensitivity inherently influences responsivity (Sih & Bell, 2008), the two are not synonymous, as behavioural responses are modulated by many contextual and individual factors. Consequently, heightened sensitivity does not invariably predict uniform behavioural outcomes. Secondly, DS can be examined from two complementary approaches: the first focuses on the developmental outcomes of individuals with heightened sensitivity, which involve long-term changes resulting from past environmental influences; whereas the second, known as Differential Reactivity (DR), captures short-term fluctuations, such as immediate behavioural or cognitive responses to stimuli. Both approaches have been empirically supported; for instance, highly sensitive children exhibit not only stronger developmental outcomes—both positive (e.g., social competence) and negative (e.g., externalizing)—in response to early parenting quality (Lionetti et al., 2019) but, also, greater positive and negative reactivity to changes in parenting quality across 7-month intervals (Slagt et al., 2018).

Slagt et al.'s longitudinal design extends beyond long-term outcomes to validate short-term reactivity as a DS marker, establishing conceptual foundations for studying DS using more dynamic methodologies. Although reviews by expert researchers (Acevedo et al., 2020; Greven et al., 2019) have recently highlighted the need for ecologically valid assessments of how high-sensitivity individuals respond to daily life events, empirical work in this area remains scarce. Only two studies have examined how trait sensitivity moderates responses to daily life experiences (Iimura, 2021; Van Reyn et al., 2023). Iimura reported findings consistent with either diathesis-stress or vantage sensitivity effects, whereas Van Reyn et al. reporting exclusively diathesis-stress effects. Nevertheless, no study has attempted to directly examine sensitivity features in the flow of daily life.

To address this gap, it is necessary to assess the dynamic nature of sensitivity (i.e., sensitivity to context) in real-life settings to (i) add critical insights into how situational and internal factors shape fluctuations in the expression of this trait, and (ii) capture their impact on the reactivity component of environmental sensitivity.

The experience sampling method (ESM) captures person × context interactions in real time, thus offering a powerful approach to assess how sensitivity and reactivity are expressed in dynamic, real-life contexts. ESM is a within-day self-assessment technique which evaluates factors such as cognition, affect, symptoms, and, importantly, contextual environmental factors as they take place (Delespaul, 1995; Myin-Germeys et al., 2018). By assessing participants in

real time and real-life, ESM offers several advantages in comparison to traditional assessment techniques such as increasing ecological validity, minimizing retrospective bias, allowing for sophisticated multi-level regression analysis, and examining the contextual basis of experiences.

The Present Study

Although the assessment of trait sensitivity has advanced, with new measures addressing the psychometric and conceptual limitations previously encountered, there is still a need for alternative methods that complement one-time retrospective assessments. Therefore, the general goal of the present study was to develop and evaluate the utility of a new set of items to examine momentary sensitivity to contextual and social factors of the environment as well as intrapersonal sensitivity. This should advance the study of the momentary contextual (e.g., nature of social situations) and personal determinants (e.g., mood states) of differential sensitivity and reactivity to context.

The study had three specific goals. First, to create a set of ESM items to assess the dimensions of sensitivity and reactivity to daily life context by (i) selecting items from established questionnaires and adapting them to a contextual framework, and (ii) developing new items especially suited for a real-life and dynamic assessment as well as other aspects of environmental experiences in daily life. Second, to qualitatively evaluate the clarity, relevance, and feasibility of these items and the ESM methodology from the perspective of participants. Third, to examine these features in both clinical and nonclinical participants through a series of focus groups integrating cognitive interviewing techniques.

Given recent evidence from our research group highlighting the significance of DS within the extended psychosis phenotype and schizotypy (Barrantes-Vidal et al., 2025a, 2025b, 2025c), and the understudied role of heightened sensitivity in this population, we prioritized the inclusion of participants from this specific clinical spectrum. Furthermore, previous findings suggest that high sensitivity is associated with creativity (Bridges & Schendan, 2019; Laros-van Gorkom et al., 2025), which itself has been proposed as an adaptive expression of psychosis liability (Fink et al., 2014; Barrantes-Vidal, 2004, 2014; Claridge & Barrantes-Vidal, 2018). Further supporting this link, polygenic risk score (PRS) studies have confirmed shared genetic markers between schizophrenia and creativity (Li et al., 2020; Kim et al., 2024), suggesting that genetic liability for mental illness may also be associated with potentially beneficial outcomes—possibly depending on environmental conditions.

2. Method

2.1.Study Overview

Candidate items were developed by adapting existing items and creating new ones specifically tailored for the real-time, dynamic assessment of sensitivity in daily life. To evaluate these items qualitatively, we employed a combination of cognitive interviewing and focus groups. This approach allowed us to obtain diverse opinions, generate discussion on different interpretations, and maintain structured attention to individual perspectives. Cognitive

interviewing is a qualitative technique used to assess and improve survey questionnaires by exploring the cognitive processes respondents use to answer questions, including comprehension, recall, judgment, and response selection (Willis, 2005). It provides validity evidence based on content by evaluating item clarity, relevance, and whether participants interpret items as intended (Dumas et al., 2008; Peterson et al., 2017). By encouraging participants to think aloud and using verbal probing—both scripted and spontaneous (Buers et al., 2014; Peterson et al., 2017)—researchers can gain in-depth insights into how items are understood, refine wording, and enhance overall validity. Cognitive interviewing and focus groups served as complementary strategies to ensure that the newly developed items were meaningful, understandable, and feasible for repeated assessment in daily life

2.2.Participants

In accordance with the recommended number of participants for an exploratory study (Krueger, 1994), a total of four focus groups were conducted: two with non-clinically evaluated university students and two with clinical participants who had a formal diagnosis of elevated risk for psychosis or a psychotic disorder. We selected clinical participants spanning differing risk states—from elevated psychosis risk to early stages of diagnosed psychotic disorders— as well as non-clinical participants allowing for a nuanced assessment of the items free of confounds (e.g., medication, stigma, biographical disruption) across the psychosis-schizotypy continuum. Clinical participants were recruited by psychiatrists and psychologists from clinical mental health centers in Barcelona, Spain. Inclusion criteria were age between 16 and 35 years old and having sufficient clinical stability to be able to engage in the discussion of items. Nonclinical focus group participants were recruited through posters, announcements in classrooms, and phone calls to participants of previous studies in the research lab. All nonclinical participants were adult university students.

For the clinical participants, we opted to include two 'mini-size focus groups' (Greenbaum, 1998; Krueger, 1994) based on the understanding that smaller groups are easier to moderate and ensure participants remain on-task, but remain large enough to generate discussion. Thus, the clinical focus groups consisted of four to five participants each, whereas the nonclinical focus groups included seven participants per group.

2.3 Procedure

2.3.1 Item Development

Item development was guided by contemporary theories of sensitivity (Aron & Aron, 1997; Pluess, 2015) and grounded in the trait definition of SPS. In addition, the development process involved examining existing ESM items from the ESM Repository (Kirtley et al., 2019) that might be useful to the study goal. Based on this, a total of 28 items tapping constructs of environmental sensitivity were identified or developed and subsequently assessed for face and construct validity with clinical psychology researchers. Guidelines were then reviewed for clarity, and construct-relevant and construct-irrelevant structure as suggested by the American Educational Research Association, the American Psychological Association, and the National Council on Measurement in Education (AERA, APA, & NCME, 2014). 17 items were deemed sub-optimal were eliminated and did not proceed to discussion in focus groups. Three items

were not assessed in the focus groups because they (i) were particularly straightforward and clear, and (ii) underwent an additional in-depth evaluation by two external experts on mentalization and intrapersonal sensitivity differences who considered them perfectly adequate These were: “Right now, my feelings are clear to me”, “Right now, I care about what other people feel/think about me”, and “Right now, I am affected by other people’s feelings (for better or for worse)”. In addition to the novel sensitivity items, a pool of four items capturing the nature of the social context appraisals was also presented to select the best options. These items are necessary for further research to (i) explore the correlates of sensitivity in the social real-world, and (ii) study how the interaction of sensitivity with social appraisals shapes the expression of mental suffering or wellbeing. A validated item capturing situational context was also included to assess its fit. This item enables calculation of reactivity by relating momentary appraisals of daily events to concurrent changes in affect (or other psychological phenomena), allowing researchers to (i) examine the dynamic expression and interplay between reactivity and sensitivity in a time- and context-dependent manner. The final list of items (n=13) assessed in the focus groups can be found in Table 1.

2.3.2 Cognitive Interviewing in Focus Groups

Ethical approval for this research was granted by the Universitat Autònoma de Barcelona (ref: 5426) and in accordance with the Declaration of Helsinski for a broader project evaluating environmental sensitivity and mental health. After informed consent was obtained from participants, the focus groups began. Focus groups of 45-60 minutes were moderated by the principal investigator of the research group, an expert in the field of psychosis, ESM, and differential susceptibility to environment. The focus groups took place in multipurpose rooms at the university and the clinical centers for the corresponding groups. The facilitator began the focus group discussions by explaining basic regulations, the purpose of the discussion, and the main concept and usage of ESM methodology. All participants received a copy of the questionnaire to facilitate discussion, as suggested by Peterson et al. (2017).

Verbal probing was the cognitive interviewing technique primarily used in our focus groups to ascertain optimal information about term and item understanding (Ericsson et al., 1993; Presser et al., 2004; Priede & Farrall, 2011). We asked questions such as, “Do you understand what this item means?”, “What do you think it means?”, and “Is the question clear?”. To determine how to best adapt items to the terminology of the target groups, we asked, “Would you change any word to make it more understandable?” (A comprehensive list of questions can be found in Table 2). Given the nature of the target questionnaire, to be asked using ESM and asked repeatedly over the course of several days, we also added “Do you think your response would change throughout the day or would it be the same?”. In addition to the evaluation of items, two more open-ended questions to address viability were included: “Do you think it would be a very effortful to answer a questionnaire like this 6 times a day for 10 days?” and “What aspects of sensitivity in daily life did we not include that you think are important to ask?” (de Thurah et al., 2023). All focus groups were recorded digitally, and notes were taken by two research team members, after acquiring consent to record from participants.

3. Results

Extensive verbal probing was used during the focus groups to target potential areas of confusion and to maintain focus on the items under discussion. The four main cognitive operations involved in item response (understanding, retrieval, judgment and response) were considered though verbal probes that principally focused on understanding of item and construct. There were observed differences in cognitive functioning and overall dynamics between the two focus groups composed of participants with a psychosis spectrum diagnosis (Groups 1 and 2). Participants in Group 1 showed good cognitive functioning. They shared introspective, thoughtful insights and were quick to understand the questions being asked. The general dynamic of the group was fluid, and they were able to interact with and follow each other's perspectives with ease. Nonetheless, one participant had more negative symptoms than the rest and did not engage as much in the general dynamic. Group 2, in comparison, presented more difficulties in understanding concepts and questions and were less able to follow each other's perspectives. Conversation often deviated to unrelated topics and personal experiences, rather than item understanding and ways to improve it. It proved more of a challenge to facilitate discussion in Group 2 than in Group 1, but overall enriching and useful information was gathered. The two nonclinical groups engaged well with the task, providing focused and articulate feedback.

3.1 Feasibility of ESM Use to Assess Sensitivity to Context

Feedback from all four focus groups was very positive for the use of ESM to evaluate sensitivity to context. Participants stressed that being asked about their environment and positive states would allow them to heighten their awareness and be more attentive to positive aspects they might miss otherwise. Importantly, they considered that this may be beneficial for their mental health. This was particularly strengthened by the clinical groups, who reflected on how positively they would find responding to questions about their wellbeing and "good experiences" rather than simply attending to their symptoms and difficulties--which is the focus of many assessments.

When participants were asked how they felt about answering a questionnaire multiple times per day over the course of several days, all groups agreed that it would depend on personal motivation. They reflected that because the questionnaires are very brief (just a few minutes per assessment), in addition to the fact that it could prompt them to reflect on their "good and bad" internal mental states, it would make the repeated questionnaires easy to answer. Furthermore, participants suggested that receiving questionnaires by text messages would make items easy to answer, although it could also present a burden at times because in modern times we are often "flooded with information." The clinical focus groups agreed that it would be more difficult to participate in an ESM study when going through an acute psychotic episode.

3.2 Item Evaluation and Refinement

Please note that in order to ease presentation of this detailed section, the results of the focus groups are followed by the description of the actions taken to resolve ambiguities based on these results.

3.2.1 Sensitivity to Context

In Group 1 differing perspectives emerged with the item “Right now, I am aware of my environment”. Half of the participants thought the item was clear, while the other half disagreed. There was considerable variability in item understanding, and numerous interpretations emerged, with general confusion about whether the item referred to internal perceptions or external stimuli. Some participants understood the item to be related to the way that they perceived reality through their senses, while others understood “aware of my environment” to mean being present in the moment or “not being in automatic mode”. One participant shared that she did not understand what it meant “to be conscious of her environment”, because “she couldn’t imagine being unconscious of her environment”, and thus it would be difficult for her to respond to this item. Similar to the perspectives pointed out in Group 1, a participant from Group 2 agreed that it was unclear if the item refers to internal perceptions or external stimuli. In general, participants in Group 2 expressed confusion when trying to explain exactly what they understood by “being aware of their environment” and concluded that there are many interpretations and that they were unable to come to an agreement about a predominant one. They, like the participants in Group 1, noted that this item would be difficult to answer. Two participants from Group 3 agreed that the question was too general. There was a divide in understanding whether the item referred to social or physical surroundings. All participants from Group 4 agreed that the item was ‘broad’. One participant suggested that the item was related to both perceptual experiences and the senses, and the majority of the other group members agreed with this interpretation. Another participant pointed out that the response would be extremely dependent on one’s feelings because “if you’re too focused on them, it changes your perception of your surroundings”. Most focus group participants across groups agreed that their response would vary throughout the day and across the course of the week, however in Group 3, a few participants believed that they would only answer differently in extreme situations “like a panic attack”, as their level of environmental awareness is generally consistent. The item was described as ambiguous and open to interpretation in all groups.

Considering this ambiguity the item was updated to: “Right now, I am aware of subtle details of my environment”. By specifying “subtle details”, we believe that the misunderstanding that participants had regarding whether the item referred to the internal or external environment was resolved. Subtle details in the environment are understood to be external details, such as the veins on the leaves of a tree (an example discussed by a participant). Further, because this item is intended to capture sensitivity to environmental context, specifying “subtle details” rather than simply referring to “awareness of” also renders the item more precise and clearer.

Regarding the items “Right now, I find beauty around me” and “Right now, I am aware of sensory stimuli (e.g., smells, lights, noise...)” there was a consensus across all groups, both clinical and non-clinical, that the items were clear and easy to understand. They agreed that their responses to these items would vary throughout the day and across different days, and added that, with the latter, they saw a possible overlap with the item “Right now, I am aware of

my environment". Note that this overlap was potentially solved after the item was revised to specify "subtle details".

For the item "Right now, I find beauty around me", it was repeatedly noted across groups that 'beauty' is a subjective, broad term that could be interpreted in purely aesthetical terms or as "something that comes from within". Further, some participants reflected that it would be a favorable experience to respond to this item numerous times a day as it would prompt them to look for beauty in their surroundings, highlighting possible reactivity to the item.

There were no problems about clarity when addressing the item "Right now, I feel too much is going on at once" in any group. One participant commented that during acute phases of psychosis, when symptoms increase in number or severity, he tended to self-isolate and lose his connection to the environment. This idea raised a debate in which all focus group members (Group 1) concurred that the response to this item and the previous ones would vary considerably under different states of their condition.

All participants agreed that the item, "Since the last beep, I have been paying attention to what I am feeling" was clear and their responses would likely vary across different days. Some participants from both the clinical and non-clinical groups commented on the reactivity of this item, suggesting that it could prompt them to actively reflect on their feelings in the moment.

Three options were presented for the final item related to contextual sensitivity: "Right now, I feel influenced by my environment", "Right now, I feel sensitive towards my environment", and "Right now, I feel sensitive to what is happening or my environment". Clinical focus group participants agreed that all versions point to "vulnerability" towards the environment. They understood this item to be related to the extent to which the environment impacts the person, rather than how the person is actively perceiving and paying attention to their environment. They also suggested that the word "environment" could be interpreted in multiple manners (e.g., social vs. physical environment). Nonclinical groups understood these items in different ways, finding important differences between the proposed items. They found the word 'influence' to be strongly related to social pressure. Similar to clinical participants in Group 1, nonclinical participants also understood the wording "I feel sensitive" to refer to vulnerability rather than perceptiveness of the environment, almost as if the environment was threatening rather than whether they were noticing details in it. It was also suggested that it would be easier to understand the phrasing "I feel sensitive" rather than "I am sensitive".

In response to this feedback, the item was revised to "Right now, I am sensitive to what is happening or my environment" to attenuate the emotional slant and threatening nature of the item described by participants. The updated phrasing shifts the focus toward perceptiveness, which may carry either a positive or negative valence, in contrast to "being influenced by the environment," which participants primarily perceived with a negative valence.

3.2.2 Situational Context

For the item, "Think about the most important event since the last beep and rate its pleasantness" (with the scale from –3: very unpleasant to +3: very pleasant), participants in Group 1 agreed that it would be difficult to find events that they considered "important" various

times a day as is standard in ESM administration. They believed that the word "important" did not suit the nature of day-to-day events, and that it should be substituted for another word. For participants in Group 2, who presented lower cognitive functioning, this item was difficult to understand, and they were confused by the chronological change as compared to other items. They struggled to switch from responding to items framed in the current moment to a retrospective response. The subjects in nonclinical groups (Groups 3 and 4) did not find difficulties with the retrospective change but agreed with clinical participants that the wording for the item was strange. Two participants from different groups pointed out that the item wording could create a tendency to focus on positive and enjoyable events.

Considering these concerns, the item was revised to "How would you rate your current situation?" This adaptation resolves the problem of shifting timelines that particularly challenged clinical Group 2 participants. By retaining the "right now" focus, the item is consistent with the rest of the questionnaire and avoids retrospective confusion created by the original "since the last beep" phrasing. In addition, removing "rate its pleasantness" and the element of "importance" from the item wording prevents participants from restricting their responses only to major or positive events. At the same time, to maintain consistency with the original measure validated by Myin-Germeys et al. (2001a), the attribution to pleasantness or unpleasantness of the experience was incorporated directly into the response scale, where –3 signifies "very unpleasant", 0 "neutral", and +3 "very pleasant."

3.2.3 Social Context

When prompted to compare the items "I feel left out" and "I am alone because people do not want to be with me", most participants from all focus groups felt that "I feel left out" was more subtle. In discussion about whether this would be difficult to answer due to feeling shame or hurt around being out of place socially, a minority of participants thought the items were equally difficult to answer. Most participants agreed that "I feel left out" was the preferred wording and psychologically easier to answer.

Based on this feedback, despite its common use in ESM research (Rauschenberg et al., 2020) to assess perceptions of the social context, the item "I am alone because people do not want to be with me," (Kwapil et al, 2009) was discarded from the final item selection due to its lack of fit for the populations of interest. While the item aimed to capture the feeling of social rejection when alone, its wording could make this experience difficult to acknowledge. Therefore, we selected the softer alternative "I feel left out" from the ESM repository (Kirtley et al., 2019), which had been presented to all focus groups and consistently favoured over the other option.

Candidate items to measure positive social appraisals, "Right now, I feel other people care about me" and "Right now, I feel that I have someone to rely on" were considered to measure different aspects. However, participants from the clinical groups agreed that having someone to support them ("rely on") was more essential than "feeling cared for". Therefore, this item was retained for the final selection. The final selection of items is presented in Table 3; the Spanish and Catalan versions are provided in Tables S1 and S2 of the supplementary material.

4. Discussion

The present study introduces a novel measure to assess sensitivity to context in daily life, offering a robust selection of items grounded in recent theoretical developments of the sensitivity concept. These items represent an important step in contemporary methodological advancements in sensitivity assessment, as they enable its systematic investigation as a dynamic, context-dependent feature, thus providing a more comprehensive understanding of the construct and its implications for mental health outcomes and well-being. Studying sensitivity in daily life also enables a more refined examination of individual differences that might significantly contribute to explain part of the large heterogeneity observed in responses to environmental exposures (Guloksuz et al., 2018). This approach aligns with contemporary frameworks such as situated psychology—a new concept grounded in multiple psychological perspectives— that frame human experience as embedded in environmental, cultural, social, and relational contexts, emphasizing the importance of capturing how psychological phenomena unfold in everyday (Birk et al., 2025). Finally, the inclusion of both clinical (individuals at risk for or with a psychotic disorder) and non-clinical (university students) populations ensures the broad applicability of the developed items, while the use of cognitive interviewing and focus groups ensures their clarity, relevance, and alignment with contemporary theoretical frameworks.

4.1 Final Selection of ESM Items Assessing Sensitivity to Context

In line with recent advancements in measuring sensitivity as a trait, our final selection of ESM items (Table 3) consisted primarily of neutrally worded items. Only two had a more explicit bias towards positive (e.g., perceiving beauty) and negative (e.g., overstimulation) aspects of sensitivity. This is particularly useful in ESM research, as it allows for the empirical examination of how different levels of sensitivity relate to positive (e.g., well-being) and negative (e.g., rumination) experiences, rather than assuming a priori that certain aspects of sensitivity are inherently positive or negative. Moreover, different aspects of sensitivity may show distinct patterns of association with positive and negative outcomes depending on individual differences in temperament and life learning history. Finally, by incorporating a more neutral or positive framing, we ensure a broader representation of the sensitivity trait, capturing the experiences of highly sensitive individuals across a broader spectrum, including those without psychological difficulties (Aron et al., 2012; Greven et al., 2019).

Our items capture the core elements of environmental sensitivity, aligning with the recently revised HSP-R scale (Pluess et al., 2024), which offers a refined and updated measure of SPS that reflects the contemporary understanding of the construct. The HSP-R accounts for an overarching General Sensitivity factor, which would align with our general items "I am sensitive to what is happening or my environment" and "I am aware of the sensory stimuli". Additionally, "I am aware of subtle details of my environment" is consistent with the Sensitivity to Details subscale of the HSP-R, whereas "I find beauty around me" aligns with Sensitivity to Positive Experiences. Conversely, the only negatively worded item, "I feel too much is going on at once", maps onto Overstimulation, highlighting the tendency to become overwhelmed by sensory input and representing the only negatively framed item in our questionnaire. The items "Since the last beep, I have been paying attention to what I am feeling" and “Right now, my feelings are clear to me” map on the Depth of Processing subscale. While items on this subscale

predominantly focus on cognitive processing (e.g., "Do you tend to reflect on things deeply?"), our item emphasizes emotional processing, which seems better suited to the multiple assessments conducted in ESM and the fact that people can appraise the processing of emotions in the moment more easily. Nonetheless, both variations capture the essence of reflection and deep engagement with internal stimuli, be it in the form of thoughts or feelings—which in fact is more an academic distinction than a mental reality. Both “Right now, I care about what other people feel/think about me” and “I am affected by other people’s feelings (for better or for worse)” capture Social Sensitivity, with the latter also capturing aspects reflected in the Emotional Reactivity subscale.

Despite this convergence with the content covered by the HSP-R scale, our item set measuring sensitivity to context does not replicate its structure exactly. Our items were designed to map on three theoretically grounded aspects of environmental sensitivity (Table 3 presents the items comprised in each dimension). Specifically, sensitivity to environmental context, captures the general components of sensitivity reflecting heightened perceptual awareness, responsiveness to external stimuli, and deeper engagement with environmental input. Intrapersonal sensitivity reflects emotional self-awareness and attention to internal states, consistent with findings that high-SPS individuals tend to exhibit greater empathy (Aron et al., 2012)—which are consistent with neurobiological findings showing increased activity in regions associated with empathy, awareness, and self-other processing (Acevedo et al., 2014, 2018). Lastly, Interpersonal Sensitivity encompasses responsiveness to others’ emotions and social evaluation, which aligns with the broader social-emotional correlates of the SPS, with research suggesting that heightened responsiveness also encompasses greater sensitivity to social cues (Wolf et al., 2011)—consistent with findings showing that high-SPS individuals exhibit stronger neural responses to social-emotional stimuli (e.g., facial expressions; Acevedo et al., 2014).

4.2 ESM Items Assessing Situational and Social Context

The study also examined how participants perceived items related to the momentary context, both social and situational.

For social context, two items capturing positive (e.g., having someone to rely on) and negative aspects (e.g., feeling left out) were considered most appropriate by participants. Evidence from ESM research indicates that a range of psychological processes—such as delusional states (Myin-Germeys et al., 2001b), heightened sensitivity to negative social interactions in bulimia (Steiger et al., 1999), and the amplification of negative bias through trait and state loneliness (Piejka et al., 2023)—are closely linked to momentary evaluations or fluctuations of the social context. This underscores the critical importance of assessing social context in daily life to examine how momentary subjective social appraisals, in interaction with individual factors (i.e., person-environment interactions), such as sensitivity, influence psychological experiences and outcomes.

For the situational context, a validated item originally developed by Myin-Germeys et al. (2001a) was assessed and subsequently adapted based on participants’ feedback. The item quantifies subjective appraisals of daily life events on a scale from –3 (very pleasant) to +3

(very unpleasant). According to the original authors, the scores can later be recoded so that higher values indicate greater perceived stress. Emotional reactivity is then derived from the strength of the association—typically estimated via multilevel regression—between these momentary stress ratings and concurrently reported levels of negative and positive affect. Unlike previous studies assessing DR in daily life that relied on retrospective reports where participants selected one key event per day (Van Reyn et al., 2023) or per week (Iimura et al., 2021) and rated their reactivity, this approach captures nuanced dynamic fluctuations in reactivity to minor stressors or fleeting positive interactions that retrospective methods might overlook.

Assessing both components of environmental sensitivity—sensitivity and reactivity—in daily life enables investigation of their dynamic expression and interplay in a time-sensitive and context-dependent manner. This approach could help explore potential bidirectional effects and determine whether DR patterns emerge under specific contextual conditions, potentially explaining why previous studies have predominantly identified either diathesis-stress or vantage sensitivity effects in isolation.

4.3 Methodological Insights: Cognitive Interviewing and Focus Group Findings

From an observational perspective, the combined use of cognitive interviewing and focus groups was a useful and informative methodology for gathering qualitative feedback for item development. As previously noted, while the potential benefits of an ESM questionnaire were recognized across all groups, some participants—particularly those from the clinical group—expressed concerns about adherence. This underscores the need to adapt ESM schedules or reduce assessment frequency to improve feasibility and minimize participants' burden, especially for clinical participants.

Another issue identified in the groups concerns the potential reactivity of specific items, namely "Right now, I find beauty around me" and "Right now, I feel too much is going on at once." Although participants often regarded this as beneficial—enhancing awareness of their environment or feelings—from a methodological standpoint it raises the possibility that repeated questioning may alter the very experiences being measured. This issue has been broadly discussed in the ESM literature (e.g., Myin-Germeys & Kuppens, 2022), though empirical evidence suggests that such effects are typically minimal; for example, studies show that repeated assessments of suicidal ideation do not exacerbate symptoms (Roth et al., 2017; Coppersmith et al., 2021) and, in some domains, similar to our participants' reflections, participants report positive effects such as increased introspection and awareness (Roth et al., 2017). Nonetheless, methodological design choices—such as sampling schemes and unpredictable prompts—can further reduce the risk of reactivity and help preserve ecological validity (Myin-Germeys & Kuppens, 2022).

4.4 Strengths and Limitations

The present study fills in an important gap in the measurement of sensitivity by devising a set of items that allow capturing sensitivity and reactivity to context in daily life, a dynamic approach that complements traditional retrospective assessments of the personality trait. Inclusion of both clinical and non-clinical participants enhances the applicability of the items

across populationsNotably, participants at risk for or diagnosed with psychosis demonstrated the capacity to reflect on their psychological experiences—a capacity often overlooked, as the psychosis label can lead to the undervaluation of personality and subtle psychological processes. Substantial variability in responses across all participants supports viewing sensitivity as a trait that is diversely distributed across individuals (Cooper, 2002), and our items appear to capture these differences even in the presence of psychopathology. A further strength is the item-development methodology, which combined focus groups with cognitive interviewing. This approach enabled both exploratory input and systematic refinement, ensuring clarity and relevance of the items while preserving individual perspectives across groups.

In regard to limitations, we only included ESM-naïve participants who had never responded to the items before, which ensured spontaneous and unbiased responses, but excluded insights from those familiar with ESM. Including experienced participants could reveal how responses might evolve with repeated exposure. Furthermore, the nonclinical sample was composed primarily of young adult university students and clinical participants who fell within the psychosis phenotype, which may restrict the generalizability of findings to broader and more diverse populations. It is also important to note that this phenotype is transdiagnostic, encompassing a wide range of manifestations that overlap with multiple disorders (van Os & Reininghaus, 2016). Further research including participants with other psychological conditions will provide complementary insights. The sample size is relatively small, although consistent with methodological recommendations for focus groups and tailored to the specific needs of this study to ensure the highest quality of the information obtained.

4.5 Conclusions, Future Directions and Implications for Psychological Assessment and Intervention

Consistent with growing evidence highlighting sensitivity as a central individual difference crucial for understanding variability in mental health (May et al., 2024), this item set was refined through focus groups to ensure it robustly captures the construct across clinical and non-clinical populations. Its development holds promise for guiding personalized assessments of person-context interactions and the design of interventions, as well as for the advancement of ecological research on how sensitivity influences mental health outcomes in real-world contexts.

While this study lays a strong foundation for measuring sensitivity to context with ecological validity, further research should employ these items in ESM designs to: (i) continue to refine and test ESM-based measures to enhance their applicability and effectiveness, (ii) examine their psychometric properties in real-life contexts, and (iii) study both the expression of sensitivity in daily life and its interaction with daily environmental experiences within the differential susceptibility framework.

An important avenue of research in clinical settings will be to examine how sensitivity influences symptom expression and remission in daily life, as well as its impact on response to interventions “for better and for worse.” Identifying which components of sensitivity are most relevant for exacerbating mental suffering and for promoting recovery and/or wellbeing in a

particular person could greatly contribute to the current goal of placing the person at the center of care, rather than prioritizing intervention protocols for “specific” clinical conditions (Assary et al., 2023).

Tables and Figures

Table 1. ESM Items Discussed in the Focus Groups.

	Presented item(s)	Preferred/Final item
Sensitivity to context	Right now, I am aware of my environment	Right now, I am aware of subtle details of my environment
	Right now, I find beauty around me	No Changes
	Right now, I am aware of the sensory stimuli (e.g., smells, lights, noise...)	No Changes
	Right now, I feel too much is going on at once	No Changes
	Since the last beep, I have been paying attention to what I am feeling	No Changes
	a. Right now, I feel influenced by my environment b. Right now, I feel sensitive towards my environment c. Right now, I feel sensitive to what is happening or my environment	Right now, *I am* sensitive to what is happening or my environment
Situational context	Think about the most important/relevant event since last beep and rate its pleasantness (-3: very unpleasant/+3: very pleasant)	How would you rate your current situation? (-3: very unpleasant/+3: very pleasant)
Social context	a. Right now, I feel other people care about me b. Right now, I feel I have someone to rely on	Right now, I feel that I have someone to rely on
	a. Right now, I am alone because people do not want to be with me b. Right now, I feel left out	Right now, I feel left out

Items labeled a, b, and c represent the options that were presented to participants in the focus groups. The 'Preferred/Final item' column indicates the items selected based on participants' feedback and consensus.

Table 2. Cognitive Interviewing and Feasibility Questions Utilized in the Focus Groups.

	Question
Verbal probing questions	
Understanding	Do you understand what this question is asking?
	What do you understand from this question?
	Is the question clear?
	Do you understand it well?
	Would you change any words or the structure of the phrase so that it is easier to understand?
Comparison	Do you think the following phrases mean the same thing?
Variability	Do you think that your answer to this question would be the same throughout the day or would vary during the day?
Adequacy	Do you think that you could answer these questions, even when there are no people around you? [a]
ESM feasibility and usage[b]	Do you see any possible benefits or concerns using ESM?
	What aspects of daily life do you believe are important to evaluate or ask about that haven't been discussed here (aspects that would be relevant for your wellbeing and on a symptom/negative experiential level)?

[a] Only asked about social interaction items. [b] Adapted from Thurah et al. (2022).

Table 3. ESM Sensitivity to Context Items**.**

	Item
Sensitivity to Environmental Context	1. Right now, I am sensitive to what is happening or my environment
	2. Right now, I am aware of the sensory stimuli (e.g., smells, lights, noise...)
	3. Right now, I am aware of subtle details of my environment
	4. Right now, I feel too much is going on at once
	5. Right now, I find beauty around me
Intrapersonal Sensitivity	6. Since the last beep, I have been paying attention to what I am feeling
	7. Right now, my feelings are clear to me
Interpersonal Sensitivity	8. Right now, I care about what other people feel/think about me
	9. Right now, I am affected by other people's feelings (for better or for worse)

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GENERAL DISCUSSION

5. GENERAL DISCUSSION

This thesis set out to test the relevance of the differential susceptibility (DS) framework for understanding individual differences in response to early environmental experiences, focusing on the extended psychosis phenotype and adopting a transdiagnostic perspective on mental health outcomes. Across six interlinked studies, it makes four interrelated contributions: a methodological infrastructure for testing DS rigorously, an exposome-based operationalization of the early environment, convergent empirical evidence for DS across two independent cohorts using both sensitivity-based and disorder-based polygenic indices, and a forward-looking ecological assessment framework for capturing sensitivity as it unfolds in daily life.

5.1. Summary of findings

Section 1 presented the development of methodological advancements to optimize testing of G×E interactions. **Chapter 1** developed a comprehensive early psychosocial exposome in the BLISS-II sample (n = 1,181), yielding a general adversity-driven factor and four specific dimensions—Positive Experiences, Paternal Adversity, Maternal Adversity, and Role Reversal. The general exposome was associated with worse outcomes across psychopathology, functioning, and positive mental health, while Positive Experiences also presented a generalized pattern of associations across all outcomes underscoring its potential in buffering psychopathology and enhancing wellbeing. Maternal and paternal adversity showed differential associations, with Maternal Adversity specifically predicting psychopathology symptoms, and Paternal Adversity associating with functional impairment, thus, revealing distinct source-specific pathways of risk. **Chapter 2** illustrates the implementation and automatization of the LEGIT package and developed a methodological pipeline integrating multiple imputation with competitive-confirmatory G×E modeling, enabling robust testing of interaction patterns in the presence of missing data.

Section 2 tested the DS model across two independent non-clinical cohorts. **Chapter 3**, conducted in the BLISS-II sample (n = 941; excluding participants without genetic data), found that PGS-ES moderated the associations between specific exposome dimensions and transdiagnostic outcomes, specifically, DS patterns emerged for the interaction between PGS-ES and Positive Experiences on both the p-factor and the Positive Mental Health factor, and for PGS-ES and Paternal Adversity on the p-factor and functioning. That is, individuals with higher PGS-ES reported greater psychopathology, poorer functioning, and lower positive mental health outcomes when exposed to fewer positive experiences or poorer paternal parenting; but also exhibited less symptoms and more positive outcomes when exposed to supportive environments compared to individuals with lower PGS-ES. These findings were partially replicated in the TwinssCan cohort (n = 638; **Chapter 4**), where significant interactions following a DS pattern were found between PGS-ES and all three environmental measures tested—adverse childhood, positive childhood and bullying—on functioning, eccentricity, and social coping abilities. Adolescents high in genetic sensitivity showed greater eccentricity, poorer adjustment, and lower social coping under adversity, and the reverse pattern under favorable conditions, compared to their lower PGS-ES counterparts. Additionally, disorder-specific Polygenic Scores—PGS-SCZ, PGS-BD, PGS-MDD, and PGS-SCZ+BD—also moderated the effects of early experiences consistent with a DS pattern: adolescents with higher

disorder-related genetic liability showed higher levels of dysfunction and eccentricity when exposed to early adverse contexts, but were also better adjusted when exposed to low adversity or high protective experiences, compared to adolescents with lower genetic liability (**Chapter 5**).

Lastly, **Section 3** presented the development of a measure to assess the dynamic expression of sensitivity in daily life. **Chapter 6** developed and qualitatively evaluated a set of ESM items to assess momentary sensitivity using focus groups mixed with cognitive interviewing across clinical and nonclinical participants. This approach ensured clarity, relevance, and ecological validity of the items and allowed for the refinement and final selection of neutrally valenced items covering three relevant dimensions: environmental, intrapersonal, and interpersonal sensitivity. Feasibility was confirmed across both groups, establishing a methodological foundation for future ecological investigation of sensitivity in daily life.

5.2. Integration of findings

Findings were partially replicated across cohorts: with broader DS effects across a wide range of psychopathology outcomes in BLISS-II (**Chapter 3**) and more restricted findings in the TwinssCan cohort (**Chapters 4 and 5).** As described in their respective chapters, this is probably due to a combination of measurement constraints, sample size differences, and more importantly, differences in developmental stage between samples; the TwinssCan cohort was predominantly adolescent ($M_{age} \approx 17$; 70% aged 15–16), a period where environmental sequelae may not yet have crystallised into differentiated symptom expressions, manifesting instead through broader indicators such as functioning and behavioural eccentricity (Hartmann et al., 2021; Shah et al., 2020). Functioning emerged consistently across cohorts and PGSs showing a DS pattern. However, whereas in TwinssCan DS effects spanned all environmental factors examined (**Chapters 4 and 5**), in BLISS-II they were circumscribed to the paternal figure (**Chapter 3**). This is likely due to how it was operationalized: whereas TwinssCan employed an observer-rated integrative measure of global adjustment capturing a wide range of adaptive and maladaptive outcomes in a non–syndrome-specific manner, in BLISS-II functioning was more focused on role performance and relational quality, domains particularly shaped by the paternal figure, whose role in children's social development and social role acquisition is well established (**see Chapters 1 and 3**).

DS effects on positive mental health outcomes were well-supported in BLISS-II yet markedly circumscribed in TwinssCan. This is again partly attributable to measurement reasons discussed in the respective chapters. Beyond that, in BLISS-II, most effects for positive mental health emerged for the Positive Experiences factor, an expected pattern given that positive experiences have been shown to exert a direct influence on well-being and resilience through mechanisms that extend beyond the mere absence of adversity (Cunha et al., 2025; Berretta et al., 2026; Bethell et al., 2019). Crucially, in BLISS-II, these positive experiences were numerous, multidimensional and integrated within a comprehensive exposome framework, whereas in TwinssCan the positive environment was restricted to a single scale capturing general upbringing quality. Such reduced scope likely contributed to the attenuated findings and highlights the importance of assessing positive experiences with granularity and across multiple domains in G×E research. Finally, the PGS-ES, being explicitly derived to index

susceptibility to the environment rather than liability to a specific phenotype, is better positioned to detect effects across the full spectrum of outcomes, including positive mental health, than disorder-specific PGSs, which, by definition, retain a stronger anchoring in psychopathological liability that may also contribute to lack of effects on this domain in **Chapter 5**.

Although the general exposome factor presented a wide range of associations with all outcome domains, including transdiagnostic psychopathology and positive mental health (**Chapter 1**), it did not yield significant G×E interactions in subsequent analyses (**Chapter 3**). This aligns with recent reviews of PGS-based G×E studies suggesting that whereas genetic liability and environmental exposures typically show robust main effects, G×E effects are smaller and more consistently detected when stressors are specific, proximal, and relational, in contrast to broader cumulative measures which tend to produce additive rather than interactive effects (Kouris & Kumsta, 2026; Illius et al., 2026). Notably, social support, interpersonal stress, and family context emerged as especially potent moderators, as illustrated by significant interactions between depression-PGS and parental criticism (Nelemans et al., 2021) or low parental bonding (Iob et al., 2023). The prominent and pervasive moderating role of parental figures as key moderators within the array of environmental factors is also consistent with the DS framework, where early caregiving has been identified as the prototypical moderating context, not because sensitivity is narrowly specific to parental relationships, but because caregiving constitutes the primary regulatory environment during the developmental windows in which sensitivity-related phenotypes are consolidated (Pluess & Belsky, 2010). That said, the presence of DS effects for peer and school-related environments in BLISS-II (**Chapter 3**) and more diffuse general adversity in TwinssCan (**Chapter 4**) supports that this genetic susceptibility extends beyond the parental dyad or nuclear family arrangement, consistent with the broader theoretical claim that highly sensitive individuals are more affected by all significant environmental inputs (Pluess & Belsky, 2010; Lionetti et al., 2019).

It has been argued that disorder-based PGSs should not, in principle, index environmental sensitivity (Zhang & Belsky, 2022) because they are derived from standard GWAS targeting variants associated with increasing the mean liability for a phenotype and therefore carry an unconditional main effect of G. However, findings in **Chapter 5** show that outcomes for which the PGS showed significant main effects in regression analyses did not show significant interaction effects, largely because they were classified as non-G×E in the competitive-confirmatory step of the LEGIT package (see **Chapter 2**), precisely because they carry a main effect of G, E, or both. Precisely, the most PGS-phenotype concordant outcomes, those related to symptomatology, showed main effects but no G×E interaction, whereas functioning, which does not map onto disorder-specific liability and constitutes a broad bipolar index spanning from superior adaptive functioning to pervasive impairment across multiple domains, consistently showed DS patterns.

Another concern is that the design of standard GWAS from which those PGSs are derived is expected to miss most G×E variants, because their effects emerge only under specific environmental exposures that tend to be unevenly distributed across population-based samples, and therefore the conditional effects of these variants are masked and their signal is diluted (Holohan & Laderman, 2020). However, the assumption that standard mean-GWAS discovery samples are approximately random with respect to environmental exposure is unlikely to hold,

especially for psychiatric disorders and psychosocial factors such as adversity, as clinical populations are characterized by a markedly elevated prevalence of adversity (see Introduction, Section 2.2). This non-random distribution would imply that variants whose effects are contingent on adversity exposure may nonetheless generate detectable signals in standard GWAS, because the adversity-exposed subgroup is systematically overrepresented among cases.

For instance, a study stratifying a GWAS for MDD by lifetime trauma exposure found that SNP-based heritability was twice as large among trauma-exposed individuals compared to non-exposed individuals (0.24 vs. 0.12), despite a genetic correlation of ~1 between the two groups (indicating that broadly the same variants underlie MDD in both groups) (Coleman et al., 2020). Although part of this heritability inflation could reflect reduced environmental variance within the trauma-exposed group, this seems unlikely to fully account for a twofold increase, suggesting that the weight of some variants increases and their signal amplifies in the exposed group because it is no longer masked by the unexposed group, in whom these variants exert no effect. A meaningful portion of MDD's polygenic architecture may therefore be environmentally contingent, and unstratified GWAS average across these heterogeneous effect profiles, diluting the G×E signal but not eliminating it. PGS derived from unstratified GWAS thus conflate environmentally contingent and independent genetic signal, and this latent environmentally contingent component might become detectable only when tested in G×E interaction models (Penner-Goeke & Binder, 2026), a pattern consistent with the dissociation of main effects and interaction effects observed in **Chapter 5**.

Overall, although this hypothesis requires further empirical testing, findings suggest that psychiatric disorder PGSs might index two components: a disorder-specific risk component comprising variants more specific to the disorder, and an unspecific plasticity component whose expression is contingent on environmental input. The latter is plausibly highly pleiotropic, and therefore transdiagnostic in scope, possibly extending to adaptive phenotypes as observed for common variants influencing genetic risk, which are extensively shared across disorders and extend to adaptive traits, as well as with the idea of a broad polygenic component exerting both risk-enhancing and risk-reducing effects across different disorders and traits (Hindley et al., 2022).

Although further empirical testing is essential, it is possible that part of this pleiotropic variation is itself environmentally contingent. This is supported by Mendelian randomization evidence showing that SNPs from a mean-GWAS for depression (Howard et al., 2019) causally predicts environmental sensitivity to depression (i.e., higher MZ twin differences in depression outcomes), indicating that variants captured by disorder GWAS partly overlap with those driving plasticity (Assary et al., 2025).

Finally, **Chapter 6** examines environmental sensitivity at the level of everyday experience. Within the integrated meta-framework of environmental sensitivity (Pluess, 2015), genetic, physiological, and behavioral sensitivity factors reflect different levels of analysis of a common underlying predisposition toward environmental responsivity—meaning that genetic and trait-level sensitivity are complementary windows onto the same phenomenon. Environmental sensitivity can therefore be captured not only at the genetic level, as presented in **Chapters 3 and 4**, but also through trait measures of sensory processing sensitivity, which has been shown

to associate broadly with psychopathological and adaptive outcomes alike (Lionetti et al., 2019; Assary et al., 2024). The ESM items developed in **Chapter 6**, grounded in contemporary sensitivity theory and validated across clinical and nonclinical participants, open the path toward examining how genetic and phenotypic plasticity converge in the dynamics of daily life.

5.3. Clinical implications

The findings of this thesis, while in need of further replication, carry several clinical implications. First, they contribute to the view that genetic liability should not be interpreted as a fixed or immutable cause of disorder, but rather as one probabilistic component within complex developmental pathways whose effects depend substantially on environmental conditions (Ellis et al., 2011; Bakermans-Kranenburg & van IJzendoorn, 2015; Gandal & Geschwind, 2021). In this sense, individuals with higher genetic susceptibility or disorder-related polygenic liability should not be conceptualized only as "at risk", but also as potentially more responsive to supportive, enriching, and therapeutic contexts. This reframing has direct implications for stigma reduction and for shifting clinical goals from risk stratification alone toward resilience-oriented, transdiagnostic prevention. Second, findings underscore the critical role of positive experiences in mental health outcomes, highlighting the importance of promoting positive peer relationships, social connectedness, adaptive coping, and resilience-building within prevention and early intervention programmes, rather than solely addressing symptom reduction and adversity. This aligns with emerging evidence supporting the potential efficacy of positive psychology interventions in reducing symptomatology, including psychotic manifestations (van Agteren et al., 2021; Pina et al., 2021), and may be particularly relevant in adolescent populations, where narrowly risk-focused approaches have shown to increase stigma, overdiagnosis, and iatrogenic harm (Foulkes & Stringaris, 2023). Third, global functioning and eccentricity emerged consistently across all disorder-related PGS examined and, although replication is needed, suggest their utility as broad behavioural markers of emerging vulnerability in adolescent populations. Monitoring such indicators may facilitate preventive support before, or as symptoms begin to emerge (Duffy et al., 2015; McGorry et al., 2018). Furthermore, the consistency of these indicators across distinct genetic liabilities points toward broad psychiatric risk pathways that may be amenable to common therapeutic targets (Gandal & Geschwind, 2021), reinforcing the value of transdiagnostic over categorical approaches. Finally, the ESM items developed in this thesis, validated in a clinical population, open an avenue for ecologically valid assessment of how environmental susceptibility unfolds dynamically in daily life, enabling personalized interventions tailored to momentary needs and strengths. Overall, clinical implications of this thesis support a shift from deterministic, risk-focused models of psychiatric genetic liability toward early, proportional interventions that address shared risk factors while fostering resilience and positive mental health.

5.4. Limitations

Several limitations deserve explicit acknowledgement beyond those addressed in individual chapters. First, while focusing on adolescents and young adults captures a developmental window critical for the peak onset of psychopathology, these findings may not generalize to other populations. Future research is required to replicate these results across larger, gender-balanced, and clinically ascertained cohorts that capture different developmental stages and

reflect greater sociodemographic heterogeneity. Second, the cross-sectional design prevents causal inferences about gene-environment interactions. Future longitudinal studies are essential to determine whether DS effects persist across development or reflect specific windows of heightened plasticity, identify critical periods when disorder-related and putative plasticity alleles exert their strongest influence, and clarify how environmental factors might shape divergent developmental pathways of risk and resilience. Third, the narrower operationalization of the environment in TwinssCan, in contrast to the exposome framework employed in BLISS-II, may have attenuated DS effects, as broader and more differentiated environmental assessment appears to yield more consistent G×E findings. Similarly, some outcomes such as internalizing symptoms and wellbeing may have been limited by restricted variance, measurement reliability, or developmental appropriateness in this cohort. Finally, a key limitation is the potential confounding of G×E effects by gene-environment correlation (rGE), as individuals' genetic predispositions may systematically co-vary with their environmental exposures, particularly when parental rearing is the environmental predictor, given that parents transmit *both* genetic predispositions and rearing environments to their offspring. In TwinssCan, linear mixed models accounting for twin pair clustering partially mitigate passive rGE. However, evocative and active rGE, where genetically influenced tendencies to evoke or select particular environments cannot be ruled out, and observed G×E effects may partly reflect these mechanisms rather than true environmental moderation. Mendelian randomization approaches could help distinguish genuine G×E from rGE-driven artefacts in future work (Spiller et al., 2019).

5.5. Future directions

The findings of this thesis point to several priorities for future research. A central direction is to identify the sets of variants and biological pathways underlying the DS patterns observed at the level of polygenic scores. Because polygenic scores aggregate variants weighted by their main effects on a disorder, they can show that genetic variation *as a whole* moderates the impact of the environment, but they cannot identify which variants carry this interaction signal or whether these variants are distinct from those driving disorder-specific risk. Addressing this requires variant-level approaches such as genome-wide environment interaction studies (GWEIS), which test SNP-by-environment effects across the genome. By estimating variant-level main and SNP×E interaction effects separately, such designs could establish whether interaction-carrying variants are separable from main-effect variants within the same PGS, and whether these SNP×E interaction effects are shared across disorders.

Multi-trait genetic analyses offer a complementary strategy to identify potential plasticity variants. Given the extensive genetic overlap between psychiatric disorders and adaptive traits, jointly modelling disorder liability and correlated positive phenotypes, such as cognitive performance, creativity, educational attainment, or adaptive personality traits, may help identify variants whose influence spans both maladaptive and adaptive outcomes. Importantly, methods to characterize mixed directions of effect among overlapping variants, such as the bivariate extension of the causal mixture model (MiXeR; Frei et al., 2019), could distinguish concordant from discordant genetic overlap. In particular, variants showing discordant cross-trait effects, that is, variants associated with higher disorder liability but also with more adaptive outcomes, represent strong candidate plasticity variants.

Finally, future research could complement genome-wide aggregate scores with biologically informed models of environmental sensitivity. Recent proposals such as the stratagenic model (García-González & O'Reilly, 2026) conceptualize genetic liability not as a single genome-wide burden but as structured across multiple, biologically distinct pathways. Applied to DS, this perspective shifts the focus from characterizing the polygenic nature of environmental sensitivity to identifying biological systems that are environmentally responsive. One promising avenue involves pathway-based PGSs, which aggregate variants according to shared biological function rather than phenotypic association (e.g., PRSet; Choi et al., 2023). Such approaches could characterize, at the genomic level, the biological systems theorized to give rise to environmental sensitivity, that is, those proposed by the Biological Sensitivity to Context theory or by sensory processing sensitivity research, such as stress-response and autonomic-regulation systems (Boyce & Ellis, 2005; Naumann et al., 2020), synaptic plasticity (Homberg et al., 2024), reward processing, or social cognition (Acevedo et al., 2014; Homberg & Jagiellowicz, 2022). Moreover, pathway-level signals could then be integrated to construct broader susceptibility profiles or clusters, identifying whether individuals carry different configurations of environmentally responsive biological systems. In line with the stratagenic model, this would allow heterogeneity in psychopathology and adaptation to be conceptualized not as variation in a *single* dimension of risk, but as differences in combinations of pathway-level susceptibilities.

Ultimately, understanding how genetic susceptibility and environmental factors jointly shape mental health outcomes requires characterizing environmental exposures with equivalent precision. In this respect, the complex, interconnected, and high-dimensional nature of environmental exposures calls for assessment approaches that capture how exposures and individual responses unfold dynamically in real life. ESM is well suited to this purpose, particularly when combined with wearable technologies, that is, sensors that passively log geospatial, physical, social, and physiological signals. Together, these tools allow the exposome to be assessed in real time, integrating objective, time-stamped indicators of how the body responds to environmental demands with subjective momentary impressions into a single longitudinal record (Turner et al., 2017). Beyond enriching digital phenotyping, this strategy speaks directly to the integration of the external and internal exposome, linking sensor-based, physical, and contextual measures to internal biological responses, which has been identified as one of the outstanding methodological challenges in the field (Manrai et al., 2017). By improving the resolution of both sides of the interaction, these complementary strategies may ultimately help uncover more robust and replicable G × E effects in psychiatric disorders.

5.6. Conclusions

The research presented in this thesis advances the understanding of differential susceptibility as a useful and valid framework for explaining individual differences in response to early environmental experiences, combining methodological innovation, exposome-based environmental assessment, and convergent evidence across independent cohorts to examine how genetic sensitivity shapes transdiagnostic mental health outcomes “for better and for worse”. Overall, the main conclusions that can be derived from this thesis are:

1. The early psychosocial exposome is suitable for mapping both the cumulative effects of early experiences and specific dimensional pathways. The source of early experiences constitutes a meaningful organizational axis, and the choice between cumulative and specific dimensional measures depends on the research goal: cumulative approaches may be better suited for detecting main or additive effects, whereas specific, proximal, and relational dimensions appear more effective for capturing G×E interactions.

2. Positive early experiences constitute an independent dimension of the early social environment, with distinct associations with psychopathology, functioning, and positive mental health over and above the general adversity factor. Critically, rather than acting exclusively as a protective factor, the absence of positive experiences independently predicts worse outcomes. This underscores the importance of their systematic inclusion in exposome research to capture the full spectrum of environmental influences on mental health.

3. Genetic sensitivity to the environment moderates the impact of both supportive and adverse early experiences on transdiagnostic psychopathology and positive mental health outcomes following a DS pattern**.** Across two independent nonclinical cohorts (BLISS-II and TwinssCan), higher PGS-ES scores were associated with worse outcomes under adverse conditions and better outcomes under favorable ones, as compared to individuals with lower PGS-ES scores.

4. Disorder-related polygenic scores for schizophrenia, bipolar disorder, major depression disorder, and shared psychotic-affective liability consistently moderated the impact of early experiences in a DS manner. DS effects across all PGS were consistent for broad transdiagnostic indicators, extending beyond their main effects on symptom domains traditionally associated with each disorder, suggesting that the common-variant polygenic architecture of psychiatric disorders encompasses not only disorder-specific risk but also a broader environmentally contingent plasticity component.

5. Individual differences in momentary sensitivity to everyday contextual variation can be adequately captured with the developed EMA items, establishing a methodological foundation for examining how sensitivity unfolds dynamically in daily life and impacts symptom dynamics and positive mental health. Individuals within the psychosis spectrum provided meaningful reflections on subtle sensitivity-related processes, and both clinical and nonclinical groups regarded the ecological assessment of environmental sensitivity as feasible and personally relevant.

6. Integrating multiple imputation within the LEGIT competitive-confirmatory framework consistently recovers higher statistical power and stronger interaction signals complete-case approaches, with efficiency gains most pronounced at higher missingness rates and smaller sample sizes, contributing to more robust and reliable G×E research.

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