ARTICLE OPEN

Check for updates

# Time to incorporate positive experiences and outcomes in psychosis research: genetic differential susceptibility to childhood experiences works for "better and for worse"

Neus Barrantes-Vidal[1,2✉], Pilar Torrecilla[1], Valeria Lavín[1], Patricia Mas-Bermejo[3], Sergi Papiol[2,4,5], Marian J. Bakermans-Kranenburg[6,7,8], Marinus H. van Ijzendoorn[9,10], Thomas R. Kwapil[11] and Araceli Rosa[2,3,12]

© The Author(s) 2025

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.

*Translational Psychiatry* (2025)15:439 ; https://doi.org/10.1038/s41398-025-03663-2

## 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

[1]Departament de Psicologia Clínica i de la Salut, Universitat Autònoma de Barcelona, Barcelona, Spain. [2]CIBER de Salud Mental, Instituto de Salud Carlos III, Madrid, Spain. [3]Secció de Zoologia i Antropologia Biològica, Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals, Universitat de Barcelona, Barcelona, Spain. [4]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich 80336, Germany. [5]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich 80336, Germany. [6]ISPA, University Institute of Psychological, Social and Life Sciences, Lisbon, Portugal. [7]Department of Psychology, Personality, Social and Developmental Psychology, Stockholm University, Stockholm, Sweden. [8]Facultad de Psicología y Humanidades, Universidad San Sebastián, Sede Valdivia, Chile. [9]Research Department of Clinical, Education and Health Psychology, Faculty of Brain Sciences, UCL, London, UK. [10]Department of Psychiatry, Monash University, Melbourne, VIC, Australia. [11]Department of Psychology, University of Illinois at Urbana-Champaign, Champaign, IL, USA. [12]Institut de Biomedicina de la UB (IBUB), Barcelona, Spain. ✉email: neus.barrantes@uab.cat

Received: 14 November 2024 Revised: 23 July 2025 Accepted: 2 October 2025
Published online: 30 October 2025

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].

## METHODS

### 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).

### Materials and procedure

*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 1000 kb 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.

*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 (Fig. 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]).

*Phenotypic measures*

Psychopathology factor (P-factor): The Multidimensional Schizotypy Scale-Brief (MSS-B) [62] assessed positive (Cronbach's $\alpha = 0.77$), negative ($\alpha = 0.70$) and disorganized ($\alpha = 0.88$) schizotypy dimensions. The Community Assessment of Psychic Experiences (CAPE) [63] assessed positive PLE ($\alpha = 0.83$). 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 ($\alpha = 0.75$) and Suspiciousness ($\alpha = 0.77$) subscales of the Schizotypal Personality Questionnaire (SPQ) [66] assessed trait paranoia. Depressive symptoms were measured using the Beck Depression Inventory (BDI; $\alpha = 0.91$) [67] and anxiety symptoms were assessed with the Beck Anxiety Inventory (BAI; $\alpha = 0.90$) [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.

Positive mental health: Three well-established measures were used: the Rosenberg Self-Esteem Scale (RSES; $\alpha = 0.88$) [69], the Connor-Davidson Resilience Scale (CD-RISC; $\alpha = 0.84$) [70], and the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS; $\alpha = 0.91$) [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: 0.973; TLI: 0.970; SRMR: 0.044; RMSEA: 0.087).

Functioning: The Social Functioning Questionnaire [72] covers aspects of both social and general functioning ($\alpha = 0.62$).

### 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




**Fig. 1 Representation of the top 6 items loading on the specific factors of the Exposome bifactor model.** 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.

procedures including k-fold cross-validation and bootstrapping were conducted to assess model stability and generalizability; details are provided in the supplementary material. The code used for data analysis is available from the corresponding author upon reasonable request.

## 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 ($p < 0.10$) and resilience ($r = 0.07$), and PGS-PLE with PLE ($r = 0.06$, for threshold $p < 0.05$), suspiciousness ($r = 0.07$–$08$, for thresholds $p < 0.05$ and $p < 0.10$ respectively) and ideas of reference ($r = 0.06$, for threshold $p < 0.10$).

### 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 $p < 0.05$ of PGS-ES interacted with Other Adverse Experiences on positive mental health and with the General Exposome factor on functioning, and only threshold $p < 0.10$ 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 $p < 0.10$) 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; Fig. 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 $p < 0.05$, these interactions indicated a vantage sensitivity strong model, in which higher PGS-ES showed less psychopathology and more positive mental health

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

| G | E | Main Outcome Domains | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Psychopathology Factor (P-factor) | | | Positive Mental Health Factor | | | Functioning | | |
| | | Est. (S.E.)[a] | F | $R^2$ | Est. (S.E.)[a] | F | $R^2$ | Est. (S.E.)[a] | F | $R^2$ |
| PGS-ES ($p < 0.05$) | 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 ($p < 0.10$) | 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 |

Interactions with $F > 1$ are **bolded**.
*PGS–ES* polygenic score of environmental sensitivity; *Est* estimate, *S.E* standard error, *Exp* experiences.
$^{**}$ $p < 0.01$, $^{+}$ $p < 0.10$.
[a]Adjusted for ancestry PC1 and PC2.

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, $p < 0.05$ (Table S4) and $p < 0.10$ (Table 2; Fig. 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 ($p < 0.10$) 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 $p < 0.05$) 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 $p < 0.10$. For interactions with threshold $p < 0.05$ 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 $p < 0.10$ threshold (Table S6).

## 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

**Table 2.** Competitive-confirmatory tests of re-parametrized regression models of Polygenic Score of Environmental Sensitivity ($p < 0.10$) interactions on main outcome domains ($n = 941$).

| **PGS-ES ($p < 0.10$) 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 ($p < 0.10$) 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 ($p < 0.10$) 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 |

In **bold**, models with lowest AIC. FollowingBelsky & Widaman [47], only models with $F > 1$ in the previous analytic step (Table 1) are examined.

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

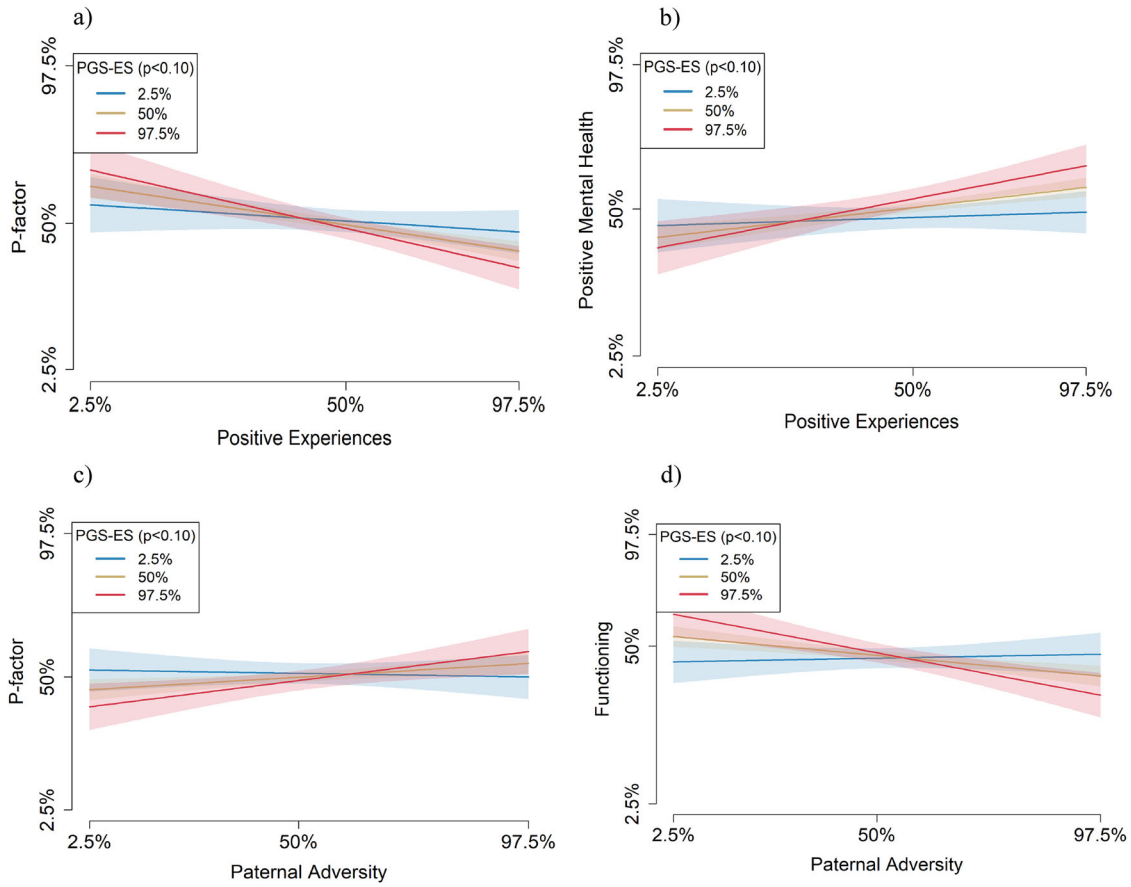



**Fig. 2 Interactions PGS-ES (p < 0.10) with F > 1 on main outcome domains.** Visual representation of the interactions between PGS-ES and Positive Experiences on **a** P-factor and **b** Positive Mental Health and interactions between PGS-ES and Paternal Adversity on **c** P-factor and **d** Functioning.

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

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

| ***Psychosis Extended Phenotype*** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **G** | **E** | **Positive Schizotypy** | | | **Negative Schizotypy** | | | **Disorganized Schizotypy** | | |
| | | **Est. (S.E.)[a]** | **F** | **$R^2$** | **Est. (S.E.)[a]** | **F** | **$R^2$** | **Est. (S.E.)[a]** | **F** | **$R^2$** |
| PGS-ES ($p < 0.05$) | 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** |
| | 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 ($p < 0.10$) | 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** |
| | 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* | | | | | | | | | | |
| **G** | **E** | **Positive PLE** | | | **Suspiciousness** | | | **Ideas of Reference** | | |
| | | Est. (S.E.)[a] | F | $R^2$ | Est. (S.E.)[a] | F | $R^2$ | Est. (S.E.)[a] | F | $R^2$ |
| PGS-ES ($p < 0.05$) | 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 |
| | 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 ($p < 0.10$) | 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 |
| | 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* | | | | | | | | | | |
| **G** | **E** | **Depression** | | | **Anxiety** | | | | | |
| | | Est. (S.E.)[a] | F | $R^2$ | Est. (S.E.)[a] | F | $R^2$ | | | |
| PGS-ES ($p < 0.05$) | F1 Positive Experiences | **−0.164 (0.106)** | **2.409** | **0.037** | −0.046 (0.097) | 0.223 | 0.019 | | | |
| | F2 Paternal Adversity | **−0.167 (0.095)$^+$** | **3.072** | **0.014** | −0.081 (0.087) | 0.864 | 0.004 | | | |
| PGS-ES ($p < 0.10$) | F1 Positive Experiences | **−0.138 (0.088)** | **2.478** | **0.037** | −0.004 (0.080) | 0.003 | 0.018 | | | |
| | F2 Paternal Adversity | **−0.138 (0.078)$^+$** | **3.117** | **0.014** | −0.046 (0.071) | 0.413 | 0.004 | | | |
| *Positive Mental Health* | | | | | | | | | | |
| **G** | **E** | **Well-being** | | | **Self-esteem** | | | **Resilience** | | |
| | | Est. (S.E.)[a] | F | $R^2$ | Est. (S.E.)[a] | F | $R^2$ | Est. (S.E.)[a] | F | $R^2$ |
| PGS-ES ($p < 0.05$) | 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 |
| | 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 (p < 0.10) | 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 |
| | 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 |

Interactions with $F > 1$ are **bolded**.
*PGS-ES* polygenic score of environmental sensitivity *Est* estimate, *S.E* standard error.
$^{**}p < 0.01$, $^+ p < 0.10$.
[a]Adjusted for ancestry PC1 and PC2.

**Table 4.** Competitive-confirmatory tests of re-parametrized regression models of Polygenic Score of Environmental Sensitivity ($p < 0.10$) interactions on individual measures (n = 941).

| **PGS-ES ($p < 0.10$) 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 ($p < 0.10$) 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 |

**Table 4.** continued

| PGS-ES ($p < 0.10$) x F1 Positive Experiences | | Positive PLE | | Disorganized Schizotypy | | Depression | |
|---|---|---|---|---|---|---|---|
| | | **AIC** | **Crossover point (95%)** | **AIC** | **Crossover point (95%)** | **AIC** | **Crossover point (95%)** |
| 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 | | |

In **bold**, models with lowest AIC. Following Belsky & Widaman [47], only models with $F > 1$ in the previous analytic step (Table 3) are examined.

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.

## DATA AVAILABILITY

Data are available upon reasonable request.

## REFERENCES

1. Walker EF, Diforio D. Schizophrenia: a neural diathesis-stress model. Psychol Rev. 1997;104:667–85. https://doi.org/10.1037/0033-295X.104.4.667.
2. Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH. For better and for worse: differential susceptibility to environmental influences. Curr Dir Psychol Sci. 2007;16:300–4. https://doi.org/10.1111/j.1467-8721.2007.00525.x.
3. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH. Differential susceptibility to the environment: an evolutionary–neurodevelopmental theory. Dev Psychopathol. 2011;23:7–28. https://doi.org/10.1017/S0954579410000611.
4. Belsky J, Pluess M. Beyond risk, resilience, and dysregulation: phenotypic plasticity and human development. Dev Psychopathol. 2013;25:1243–61. https://doi.org/10.1017/S095457941300059X.
5. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes?. Mol Psychiatry. 2009;14:746–54. https://doi.org/10.1038/mp.2009.44.
6. Pluess M, Belsky J. Vantage sensitivity: individual differences in response to positive experiences. Psychol Bull. 2013;139:901–16. https://doi.org/10.1037/a0030196.

7. Bakermans-Kranenburg MJ, van IJzendoorn MH. The hidden efficacy of interventions: gene × environment experiments from a differential susceptibility perspective. Annu Rev Psychol. 2015;66:381–409. https://doi.org/10.1146/annurev-psych-010814-015407.
8. McLaughlin KA, Gabard-Durnam L. Experience-driven plasticity and the emergence of psychopathology: a mechanistic framework integrating development and the environment into the Research Domain Criteria (RDoC) model. J Psychopathol Clin Sci. 2022;131:575–87. https://doi.org/10.1037/abn0000598.
9. Walker EF, Aberizk K, Yuan E, Bilgrami Z, Ku BS, Guest RM. Developmental perspectives on the origins of psychotic disorders: The need for a transdiagnostic approach. Dev Psychopathol. 2024;36:2559–69. https://doi.org/10.1017/S0954579424000397.
10. Debbané M, Barrantes-Vidal N. Schizotypy from a developmental perspective. Schizophr Bull. 2015;41(suppl 2):S386–95. https://doi.org/10.1093/schbul/sbu175.
11. Smoller JW, Andreassen OA, Edenberg HJ, Faraone SV, Glatt SJ, Kendler KS. Psychiatric genetics and the structure of psychopathology. Mol Psychiatry. 2019;24:409–20. https://doi.org/10.1038/s41380-017-0010-4.
12. Zheutlin AB, Dennis J, Karlsson Linnér R. Penetrance and pleiotropy of polygenic risk scores for schizophrenia in 106,160 patients across four health care systems. Am J Psychiatry. 2019;176:846–55. https://doi.org/10.1176/appi.ajp.2019.18121287.
13. Sideli L, Murray RM, Schimmenti A, Brambilla P, Fisher HL, Koenen KC, et al. Childhood adversity and psychosis: a systematic review of bio-psycho-social mediators and moderators. Psychol Med. 2020;50:1761–82. https://doi.org/10.1017/S0033291720002172.
14. Butler R, Berry K, Varese F, Bucci S. Are family warmth and positive remarks related to outcomes in psychosis? A systematic review. Psychol Med. 2019;49:1250–65. https://doi.org/10.1017/S0033291718003768.
15. Szöke A, Pignon B, Schürhoff F. Schizophrenia risk factors in exceptional achievers: a re-analysis of a 60-year-old database. Sci Rep. 2019;9:1294. https://doi.org/10.1038/s41598-018-37484-9.
16. Power RA, Steinberg S, Bjornsdottir G, Rietveld CA, Abdellaoui A, Nivard MG, et al. Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. Nat Neurosci. 2015;18:953–5. https://doi.org/10.1038/nn.4040.
17. Barrantes-Vidal N. Creativity and madness revisited from current psychological perspectives. J Conscious Stud. 2004;11:58–78.
18. Barrantes-Vidal N Creativity and the spectrum of affective and schizophrenic psychoses. In: Kaufman JC, editor. Creativity and mental illness. Cambridge University Press; 2014. pp. 169–204.
19. Claridge G, Barrantes-Vidal N Creativity: A healthy side of madness. In: Claridge G, editor. Psychopathology and Personality Dimensions. Routledge; 2018. pp. 192–204.
20. Kwapil TR, Barrantes-Vidal N. Schizotypy: looking back and moving forward. Schizophr Bull. 2015;41(Suppl 2):S366–73. https://doi.org/10.1093/schbul/sbu186.
21. Barrantes-Vidal N, Grant P, Kwapil TR. The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. Schizophr Bull. 2015;41(Suppl 2):S408–16. https://doi.org/10.1093/schbul/sbu191.
22. Guloksuz S, van Os J. The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. Psychol Med. 2018;48:229–44. https://doi.org/10.1017/S0033291717001775.
23. Barrantes-Vidal N, Kwapil TR Conceptualization and assessment of multidimensional schizotypy. In: Cheli S, Lysaker PH, editors. A dimensional approach to schizotypy: Conceptualization and treatment. Springer Nature; 2023. p. 81–96.
24. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry. 2016;15:118–24. https://doi.org/10.1002/wps.20310.
25. Cuthbert BN. Translating intermediate phenotypes to psychopathology: the NIMH research domain criteria. Psychophysiology. 2014;51:1205–6. https://doi.org/10.1111/psyp.12342.
26. Kotov R, Krueger RF, Watson D, Achenbach TM, Althoff RR, Bagby RM, et al. The hierarchical taxonomy of psychopathology (HiTOP): a dimensional alternative to traditional nosologies. J Abnorm Psychol. 2017;126:454–77. https://doi.org/10.1037/abn0000258.
27. Caspi A, Moffitt TE. All for one and one for all: mental disorders in one dimension. Am J Psychiatry. 2018;175:831–44. https://doi.org/10.1176/appi.ajp.2018.17121383.
28. Watts AL, Greene AL, Bonifay W, Fried EI. A critical evaluation of the p-factor literature. Nat Rev Psychol. 2024;3:108–22. https://doi.org/10.1038/s44159-023-00260-2.
29. Kemp KC, Bathery AJ, Barrantes-Vidal N, Kwapil TR. Positive, negative, and disorganized schizotypy predict differential patterns of interview-rated schizophrenia-spectrum symptoms and impairment. Assessment. 2021;28:141–52. https://doi.org/10.1177/1073191119900008.
30. Keyes CLM. The mental health continuum: from languishing to flourishing in life. J Health Soc Behav. 2002;43:207–22. https://doi.org/10.2307/3090197.
31. Iasiello M, Van Agteren J. Mental health and/or mental illness: a scoping review of the evidence and implications of the dual-continua model of mental health. Evid Base. 2020;1:1–45. https://doi.org/10.21307/eb-2020-001.
32. Yang H, Gao S, Li J, Yu H, Xu J, Lin C, et al. Remission of symptoms is not equal to functional recovery: psychosocial functioning impairment in major depression. Front Psychiatry. 2022;13:915689 https://doi.org/10.3389/fpsyt.2022.915689.
33. McKay MT, Kilmartin L, Meagher A, Cannon M, Healy C, Clarke MC. A revised and extended systematic review and meta-analysis of the relationship between childhood adversity and adult psychiatric disorder. J Psychiatr Res. 2022;153:1–12. https://doi.org/10.1016/j.jpsychires.2022.06.030.
34. Rosenfield PJ, Jiang D, Pauselli L. Childhood adversity and psychotic disorders: epidemiological evidence, theoretical models and clinical considerations. Schizophr Res. 2022;247:55–66. https://doi.org/10.1016/j.schres.2021.06.005.
35. Sheinbaum T, Gizdic A, Kwapil TR, Barrantes-Vidal N. A longitudinal study of the impact of childhood adversity dimensions on social and psychological factors and symptoms of psychosis, depression, and anxiety. Schizophr Res. 2024;270:102–10. https://doi.org/10.1016/j.schres.2024.05.016.
36. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomark Prev. 2005;14:1847–50. https://doi.org/10.1158/1055-9965.EPI-05-0456.
37. Guloksuz S, van Os J, Rutten BPF. The exposome paradigm and the complexities of environmental research in psychiatry. JAMA Psychiatry. 2018;75:985–6. https://doi.org/10.1001/jamapsychiatry.2018.1211.
38. Pries LK, Lage-Castellanos A, Delespaul P, Kenis G, Luykx JJ, Lin BD, et al. Estimating exposome score for schizophrenia using predictive modeling approach in two independent samples: the results from the EU-GEI study. Schizophr Bull. 2019;45:960–5. https://doi.org/10.1093/schbul/sbz054.
39. Pries LK, Erzin G, van Os J, Ten Have M, de Graaf R, van Dorsselaer S, et al. Predictive performance of exposome score for schizophrenia in the general population. Schizophr Bull. 2021;47:277–83. https://doi.org/10.1093/schbul/sbaa170.
40. Barzilay R, Pries LK, Moore TM, Gur RE, van Os J, Rutten BPF, et al. Exposome and trans-syndromal developmental trajectories toward psychosis. Biol Psychiatry Glob Open Sci. 2022;2:197–205. https://doi.org/10.1016/j.bpsgos.2022.05.001.
41. Thakkar KN, McCleery A, Minor KS, Lee J, Humpston CS, Chopik WJ, et al. Moving from risk to resilience in psychosis research. Nat Rev Psychol. 2023;2:537–55. https://doi.org/10.1038/s44159-023-00205-9.
42. Barrantes-Vidal N, Torrecilla P, Mas-Bermejo P, Papiol S, Bakermans-Kranenburg MJ, van IJzendoorn MH, et al. Genetic susceptibility to the environment moderates the impact of childhood experiences on psychotic, depressive, and anxiety dimensions. Schizophr Bull. 2025a;51:S95–S106. https://doi.org/10.1093/schbul/sbad130.
43. Barrantes-Vidal N, Torrecilla P, Mas-Bermejo P, Papiol S, Bakermans-Kranenburg MJ, van IJzendoorn MH, et al. Genetic individual differences in reactivity to the environment impact psychotic and affective reactivity in daily-life. Schizophr Bull. 2025b;51:S74–S84. https://doi.org/10.1093/schbul/sbad162.
44. Keers R, Coleman JR, Lester KJ, Roberts S, Breen G, Thastum M, et al. A genome-wide test of the differential susceptibility hypothesis reveals a genetic predictor of differential response to psychological treatments for child anxiety disorders. Psychother Psychosom. 2016;85:146–58. https://doi.org/10.1159/000444023.
45. Legge SE, Jones HJ, Kendall KM, Pardiñas AF, Menzies G, Bracher-Smith M, et al. Association of genetic liability to psychotic experiences with neuropsychotic disorders and traits. JAMA Psychiatry. 2019;76:1256–65. https://doi.org/10.1001/jamapsychiatry.2019.2508.
46. Widaman KF, Helm JL, Castro-Schilo L, Pluess M, Stallings MC, Belsky J. Distinguishing ordinal and disordinal interactions. Psychol Methods. 2012;17:615–22. https://doi.org/10.1037/a0030003.
47. Belsky J, Widaman K. Editorial perspective: Integrating exploratory and competitive-confirmatory approaches to testing person × environment interactions. J Child Psychol Psychiatry. 2018;59:296–8. https://doi.org/10.1111/jcpp.12824.
48. van Os J, Pries LK, Ten Have M, de Graaf R, van Dorsselaer S, Delespaul P, et al. Evidence, and replication thereof, that molecular-genetic and environmental risks for psychosis impact through an affective pathway. Psychol Med. 2022;52:1910–22. https://doi.org/10.1017/S0033291720003748.
49. Gibson LE, Alloy LB, Ellman LM. Trauma and the psychosis spectrum: a review of symptom specificity and explanatory mechanisms. Clin Psychol Rev. 2016;49:92–105. https://doi.org/10.1016/j.cpr.2016.08.003.
50. Chapman LJ, Chapman JP. Infrequency scale for personality measures. Unpublished scale available from T. R. Kwapil, UIUC Department of Psychology, Champaign, IL, 61820;1983.
51. The 1000 Genomes Project Consortium. A global reference for human genetic variation. Nature. 2015;526:68–74. https://doi.org/10.1038/nature15393.

52. Lemery-Chalfant K, Clifford S, Dishion TJ, Shaw DS, Wilson MN. Genetic moderation of the effects of the family check-up intervention on children's internalizing symptoms: a longitudinal study with a racially/ethnically diverse sample. Dev Psychopathol. 2018;30:1729–47. https://doi.org/10.1017/S095457941800127X.
53. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, et al. Development and validation of a brief screening version of the childhood trauma questionnaire. Child Abus Negl. 2003;27:169–90. https://doi.org/10.1016/s0145-2134(02)00541-0.
54. Li M, Cassis T, D'Arcy C, Low N, Meng X. Development and validation of a brief form of the childhood adversities questionnaire among a population of mood disorders. J Interpers Violence. 2020;37:NP2288–NP2312. https://doi.org/10.1177/0886260520933037.
55. Parker G, Tupling H, Brown L. A parental bonding instrument. Br J Med Psychol. 1979;52:1–10. https://doi.org/10.1037/t06510-000.
56. Bethell C, Jones J, Gombojav N, Linkenbach J, Sege R. Positive childhood experiences and adult mental and relational health in a statewide sample: associations across adverse childhood experiences levels. JAMA Pediatr. 2019;173:e193007 https://doi.org/10.1001/jamapediatrics.2019.3007.
57. Narayan AJ, Rivera LM, Bernstein RE, Harris WW, Lieberman AF. Positive childhood experiences predict less psychopathology and stress in pregnant women with childhood adversity: A pilot study of the benevolent childhood experiences (BCEs) scale. Child Abus Negl. 2018;78:19–30. https://doi.org/10.1016/j.chiabu.2017.09.022.
58. Crush E, Arseneault L, Moffitt TE, Danese A, Caspi A, Jaffee SR, et al. Protective factors for psychotic experiences amongst adolescents exposed to multiple forms of victimization. J Psychiatr Res. 2018;104:32–8. https://doi.org/10.1016/j.jpsychires.2018.06.011.
59. Moore TM, Reise SP, Depaoli S, Haviland MG. Iteration of partially specified target matrices: applications in exploratory and Bayesian confirmatory factor analysis. Multivariate Behav Res. 2015;50:149–61. https://doi.org/10.1080/00273171.2014.973990.
60. Moore TM, Visoki E, Argabright ST, Didomenico GE, Sotelo I, Wortzel JD, et al. Modeling environment through a general exposome factor in two independent adolescent cohorts. Exposome. 2022;2:osac010. https://doi.org/10.1093/exposome/osac010.
61. Lavín V, Torrecilla P, Fagián-Nuñez K, Kwapil TR, Barrantes-Vidal N. Integration of positive environmental factors and differentiation of parental figures in exposome research. Front Psychol. 2025. In Press. https://doi.org/10.3389/fpsyg.2025.1655172.
62. Gross GM, Kwapil TR, Raulin ML, Silvia PJ, Barrantes-Vidal N. The multidimensional schizotypy scale-brief: scale development and psychometric properties. Psychiatry Res. 2018;261:7–13. https://doi.org/10.1016/j.psychres.2017.12.033.
63. Stefanis NC, Hanssen M, Smirnis NK, Avramopoulos DA, Evdokimidis IK, Stefanis CN, et al. Evidence that three dimensions of psychosis have a distribution in the general population. Psychol Med. 2002;32:347–58. https://doi.org/10.1017/S0033291701005141.
64. Rubin DB Multiple imputation for nonresponse in surveys. John Wiley & Sons Inc.; 1987. https://doi.org/10.1002/9780470316696.
65. Baranzini D The "Bar Procedure": Single data-file compressing SPSS multiply imputed files; 2018. Available from: https: //www.researchgate.net/publication/328887514_SPSS_Single_dataframe_aggregating_SPSS_Multiply_Imputed_split_files. Accessed October 8, 2025.
66. Raine A. The SPQ: A scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull. 1991;17:555–64. https://doi.org/10.1093/schbul/17.4.555.
67. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-571. https://doi.org/10.1001/archpsyc.1961.01710120031004
68. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56:893–7. https://doi.org/10.1037/0022-006X.56.6.893.
69. Rosenberg M Society and the adolescent self-image. Princeton, NJ: Princeton University Press; 1965. https://doi.org/10.1037/t01038-000.
70. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the connor-davidson resilience scale (cd-risc): validation of a 10-item measure of resilience. J Trauma Stress. 2007;20:1019–28. https://doi.org/10.1002/jts.20271.
71. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, et al. The warwick-edinburgh mental well-being Scale (WEMWBS): development and UK validation. Health Qual Life Outcomes. 2007;5:63. https://doi.org/10.1186/1477-7525-5-63.
72. Tyrer P, Nur U, Crawford M, Karlsen S, MacLean C, Rao B, et al. The social functioning questionnaire: a rapid and robust measure of perceived functioning. Int J Soc Psychiatry. 2005;51:265–75. https://doi.org/10.1177/0020764005057391.
73. Jolicoeur-Martineau A, Belsky J, Szekely E, Widaman KF, Pluess M, Greenwood C, et al. Distinguishing differential susceptibility, diathesis-stress, and vantage sensitivity: beyond the single gene and environment model. Dev Psychopathol. 2020;32:73–83. https://doi.org/10.1017/S0954579418001438.
74. Zhang X, Sayler K, Hartman S, Belsky J. Infant temperament, early-childhood parenting, and early-adolescent development: testing alternative models of parenting × temperament interaction. Dev Psychopathol. 2022;34:784–95. https://doi.org/10.1017/S0954579420002096.
75. Belsky J, Pluess M, Widaman KF. Confirmatory and competitive evaluation of alternative gene-environment interaction hypotheses. J Child Psychol Psychiatry. 2013;54:1135–43. https://doi.org/10.1111/jcpp.12075.
76. Akaike H Information theory and an extension of the maximum likelihood principle. In: Parzen E, Tanabe K, Kitagawa G, editors. Selected Papers of Hirotugu Akaike. Springer; 1998. pp. 199–213. https://doi.org/10.1007/978-1-4612-1694-0_15.
77. Burnham KP, Anderson DR Model selection and inference: a practical information-theoretic approach. 2nd ed. New York, NY: Springer; 2002. https://doi.org/10.1007/b97636.
78. McMahon EM, Corcoran P, Keeley H, Clarke M, Coughlan H, Wasserman D, et al. Risk and protective factors for psychotic experiences in adolescence: a population-based study. Psychol Med. 2021;51:1220–8. https://doi.org/10.1017/S0033291719004136.
79. Karcher NR, Paul SE, Johnson EC, Hatoum AS, Baranger DAA, Agrawal A, et al. Psychotic-like experiences and polygenic liability in the adolescent brain cognitive development study. Biol Psychiatry Cogn Neurosci Neuroimaging. 2022;7:45–55. https://doi.org/10.1016/j.bpsc.2021.06.012.
80. Ku BS, Ren J, Compton MT, Druss BG, Guo S, Walker EF. The association between neighborhood-level social fragmentation and distressing psychotic-like experiences in early adolescence: the moderating role of close friends. Psychol Med. 2022;52:663–71. https://doi.org/10.1017/S0033291724000278.
81. Danoff JS, Wroblewski KL, Graves AJ, Quinn GC, Perkeybile AM, Kenkel WM, et al. Genetic, epigenetic, and environmental factors controlling oxytocin receptor gene expression. Clin Epigenet. 2021;13:23 https://doi.org/10.1186/s13148-021-01017-5.
82. Van IJzendoorn MH, Bakermans-Kranenburg MJ Matters of significance. In: Replication, translation, and academic freedom in developmental science. London: UCL PRESS; 2024. ISBN: 9781800086500.
83. Dong Q, Ma Q, Wang W, Wang J, Pluess M, Ma X. Environmental sensitivity moderates the longitudinal effect of fathers' positive parenting on mental disorders in chinese adolescents. J Affect Disord. 2024;366:153–61. https://doi.org/10.1016/j.jad.2024.08.178.
84. Möller EL, Nikolić M, Majdandžić M, Bögels SM. Associations between maternal and paternal parenting behaviors, anxiety and its precursors in early childhood: a meta-analysis. Clin Psychol Rev. 2016;45:17–33. https://doi.org/10.1016/j.cpr.2016.03.002.
85. Feldman R. Father contribution to human resilience. Dev Psychopathol. 2023;35:2402–19. https://doi.org/10.1017/S0954579423000354.
86. Yaffe Y. Systematic review of the differences between mothers and fathers in parenting styles and practices. Curr Psychol. 2023;42:16011–24. https://doi.org/10.1007/s12144-020-01014-6.
87. Gámez-Guadix M, Almendros C. Parental discipline in Spain and in the United States: differences by country, parent-child gender and education level. Infancia y Aprendiz. 2015;38:569–99. https://doi.org/10.1080/02103702.2015.1054665.
88. Rikhye K, Tyrka AR, Kelly MM, Gagne GG Jr, Mello AF, Mello MF, et al. Interplay between childhood maltreatment, parental bonding, and gender effects: impact on quality of life. Child Abus Negl. 2008;32:19–34. https://doi.org/10.1016/j.chiabu.2007.04.012.
89. Bacikova-Sleskova M, Barbierik L, Orosová O. Perceived parental control, parent-adolescent relationship and adolescents' psychological adjustment: does gender matter?. J Child Fam Stud. 2024;33:1632–46. https://doi.org/10.1007/s10826-023-02643-8.
90. Yogman MW, Eppel AM The role of fathers in child and family health. In: Grau Grau M, las Heras Maestro M, Riley Bowles H, editors. *Engaged fatherhood for men, families and gender equality: healthcare, social policy, and work perspectives*. Springer; 2022. https://doi.org/10.1007/978-3-030-75645-1_2.
91. Kemp KC, Burgin CJ, Raulin ML, Kwapil TR. Using multiple measures of openness to experience to capture positive, negative, and disorganized dimensions of schizotypy. Personality Disord. 2020;11:260–9. https://doi.org/10.1037/per0000389.
92. McGorry P, van Os J. Redeeming diagnosis in psychiatry: timing versus specificity. Lancet. 2013;381:343–5. https://doi.org/10.1016/S0140-6736(12)61268-9.
93. Valiente C, Romero N, Hervas G, Espinosa R. Evaluative beliefs as mediators of the relationship between parental bonding and symptoms of paranoia and depression. Psychiatry Res. 2014;215:75–81. https://doi.org/10.1016/j.psychres.2013.10.014.

94. Schönig SN, Thompson E, Kingston J, Gaudiano BA, Ellett L, Krkovic K. The apple doesn't fall far from the tree? paranoia and safety behaviours in adolescent-parent-dyads. Res Child Adolesc Psychopathol. 2024;52:267–75. https://doi.org/10.1007/s10802-023-01128-y.
95. McLaughlin KA, Sheridan MA. Beyond cumulative risk: a dimensional approach to childhood adversity. Curr Dir Psychol Sci. 2016;25:239–45. https://doi.org/10.1177/0963721416655883.
96. Zhang X, Belsky J. Three phases of gene × environment interaction research: theoretical assumptions underlying gene selection. Dev Psychopathol. 2022;34:295–306. https://doi.org/10.1017/S0954579420000966.
97. Francis ER, Tsaligopoulou A, Stock SE, Pingault JB, Baldwin JR. Subjective and objective experiences of childhood adversity: a meta-analysis of their agreement and relationships with psychopathology. J Child Psychol Psychiatry. 2023;64:1185–99. https://doi.org/10.1111/jcpp.13803.
98. Runze J, van IJzendoorn MH. Response bias is genetically biased: another argument for kagan's philippic against questionnaires in developmental psychology. Dev Psychol. 2023. https://doi.org/10.1037/dev0001614.
99. Assary E, Krebs G, Eley TC. Practitioner review: differential susceptibility theory: might it help in understanding and treating mental health problems in youth?. J Child Psychol Psychiatry. 2023;64:1104–14. https://doi.org/10.1111/jcpp.13801.
100. Harrop C, Ellett L, Brand R, Lobban F. Friends interventions in psychosis: a narrative review and call to action. Early Inter Psychiatry. 2015;9:269–78. https://doi.org/10.1111/eip.12172.
101. Homberg JR, Jagiellowicz J. A neural model of vulnerability and resilience to stress-related disorders linked to differential susceptibility. Mol Psychiatry. 2022;27:514–24. https://doi.org/10.1038/s41380-021-01047-8.
102. Homberg JR, Brivio P, Greven CU, Calabrese F. Individuals being high in their sensitivity to the environment: are sensitive period changes in play?. Neurosci Biobehav Rev. 2024;159:105605. https://doi.org/10.1016/j.neubiorev.2024.105605.
103. Keshavan MS, Clementz BA. Precision medicine for psychosis: a revolution at the interface of psychiatry and neurology. Nat Rev Neurol. 2023;19:193–4. https://doi.org/10.1038/s41582-023-00788-0.

## ACKNOWLEDGEMENTS

The study was supported by the Spanish Ministry of Science and Innovation MCIN/AEI/10.13039/501100011033 (PID2020-119211RB-I00) and the Generalitat de Catalunya (2021SGR00706 and 2021SGR01010). NBV was supported by the ICREA Academia Award of the Generalitat de Catalunya. PMB was funded by the PhD scholarship program FI-SDUR (2021-FISDU-00032) from Agencia de Gestión de Ayudas Universitarias y de Investigación (AGAUR). VL was supported by the Spanish Ministry of Science and Innovation (PRE2021-097443). The genotyping service was carried out at the Genotyping Unit-CEGEN in the Spanish National Cancer Research Centre (CNIO), supported by Instituto de Salud Carlos III (ISCIII), Ministerio de Ciencia e Innovación. CEGEN is part of the initiative IMPaCT-GENóMICA (IMP/00009) cofunded by ISCIII and the European Regional Development Fund (ERDF).

## AUTHOR CONTRIBUTIONS

NBV: conceptualization, methodology, supervision, funding acquisition, resources, data curation, investigation, project administration, writing-original draft, writing-review and editing. PT: formal analyses, writing-original draft, writing-review and editing. VL: formal analyses, writing-review and editing. PMB: formal analyses, writing-review and editing. SP: formal analyses, writing-review and editing. MBK: methodology, validation, writing-review and editing. MVI: methodology, validation, writing-review and editing. TRK: methodology, writing-review and editing. AR: resources, data curation, supervision, writing-review and editing.

## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICS STATEMENT

All participants provided written informed consent. 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).

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1038/s41398-025-03663-2.

**Correspondence** and requests for materials should be addressed to Neus Barrantes-Vidal.

**Reprints and permission information** is available at http://www.nature.com/reprints

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

© The Author(s) 2025