Archival Report

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Exposome-Wide Gene-By-Environment Interaction Study of Psychotic Experiences in the UK Biobank

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ABSTRACT

BACKGROUND: A previous study successfully identified 148 of 23,098 exposures associated with any psychotic experiences (PEs) in the UK Biobank using an exposome-wide association study (XWAS). Furthermore, research has shown that the polygenic risk score for schizophrenia (PRS-SCZ) is associated with PEs. However, the interaction of these exposures with PRS-SCZ remains unknown.

METHOD: To systematically investigate possible gene-by-environment interactions underlying PEs through data-driven agnostic analyses, we conducted 1) conditional XWAS adjusting for PRS-SCZ to estimate the main effects of the exposures and of PRS-SCZ, 2) exposome-wide interaction study (XWIS) to estimate multiplicative and additive interactions between PRS-SCZ and exposures, and 3) correlation analyses between PRS-SCZ and exposures. The study included 148,502 participants from the UK Biobank.

RESULTS: In the conditional XWAS models, significant effects of PRS-SCZ and 148 exposures on PEs remained statistically significant. In the XWIS model, we found significant multiplicative (multiplicative scale, 1.23; 95% CI, 1.10–1.37; $p = 4.0 \times 10^{-4}$) and additive (relative excess risk due to interaction, 0.55; 95% CI, 0.32–0.77; synergy index, 0.22; 95% CI, 0.14–0.30; and attributable proportion, 1.59; 95% CI, 1.30–1.91; all $ps < .05/148$) interactions of PRS-SCZ and the variable serious medical conditions/disability with PEs. We additionally identified 6 additive gene-by-environment interactions for mental distress, help-/treatment-seeking behaviors (3 variables), sadness, and sleep problems. In the correlation test focused on 7 exposures that exhibited significant interactions with PRS-SCZ, nonsignificant or small ($r < 0.04$) gene-by-environment correlations were observed.

CONCLUSIONS: These findings reveal evidence for gene-by-environment interactions underlying PEs and suggest that intertwined pathways of genetic vulnerability and exposures may contribute to psychosis risk.

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Psychotic experiences (PEs) are common and disabling conditions, comprising delusions (unreal beliefs or impressions) or hallucinations (unreal visual or auditory perceptions) in people who do not fulfill the criteria for psychotic disorders. They have a lifetime prevalence of 5% to 10% in the general population (1). Behavioral, genetic, and epidemiological research has found that PEs may represent subtle, subclinical symptoms across the psychosis spectrum and often precede or accompany the onset of clinical psychosis (2). Longitudinal studies and familial aggregation research suggest substantial overlap between PEs and the development of schizophrenia (SCZ) spectrum disorders (3,4). PEs are moderately heritable and show considerable environmental influence (5). Understanding the genetic and environmental mechanisms of PEs is crucial for the development of tailored prevention, targeted interventions, and the improvement of clinical outcomes in individuals with mental disorders.

Hypothesis-driven research has identified several environmental factors associated with psychosis such as bullying (6), stressful life events (7), cannabis use (8), tobacco use (9), and low birth weight (10), as well as less studied exposures such as physical activity (11), toxins (12), and nutrients. However, these one-exposure-to-one-outcome hypothesis-testing studies fail to embrace the multiplicity of (and complex relationships among) exposures and are prone to selective reporting and publication bias, which involve arbitrary decisions. The availability of large public datasets, together with increased transparency in data processing and standardized analytical algorithms, has significantly advanced agnostic data-driven approaches in human epidemiology. A recent exposome-wide analysis of PEs in the UK Biobank (UKB) has confirmed previous environmental factors associated with PEs, as well as factors that had not been considered to date, such as major dietary changes in the last 5 years and playing computer games (13).

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While twin studies suggest moderate heritability of PEs, the contribution of common genetic variants (as measured by single nucleotide polymorphism (SNP) heritability) to PEs is considered relatively small, with a SNP heritability <2% (14,15), especially compared with clinical psychotic disorders. Although a genome-wide association study (GWAS) of PEs identified genome-wide significant loci, none showed evidence of colocalization with SCZ (16). Significant genetic correlations (r_g) between PEs and psychiatric diseases such as SCZ have been detected. However, findings of studies investigating the associations between PEs and the polygenic risk score (PRS) for SCZ (PRS-SCZ) have been inconsistent, showing no (17,18), weak (15,16), or significant (19,20) positive associations. These studies might have been limited by the statistical power of GWAS and target sample size. Therefore, the genetic association of PRS-SCZ with PEs remains to be verified using the most recent SCZ GWAS (21).

In a twin study of PEs (20), the heritability of PEs decreased with increasing environmental exposure, highlighting the importance of a diathesis-stress or bioecological framework for understanding adolescent PEs. Previous candidate gene-by-environment (G×E) interaction studies of PEs yielded inconsistent results (22–25). The advent of PRSs, which aggregate genome-wide common variants to index a person's genetic propensities for a trait, has created opportunities for testing G×E interactions. Recent G×E interaction studies that tested the interaction of PRS-SCZ with high birth weight (26) and smoking (27) also need to be replicated. Here, we conducted the first systematic and agnostic exposome-wide interaction analyses to identify G×E interactions underlying PEs.

METHODS AND MATERIALS

Sample

The current study included participants from the UKB, a large, prospective, population-based cohort that included around half a million participants from the United Kingdom (28). All participants provided written informed consent, and ethical approval was given by the National Research Ethics Service Committee North West Multi-Centre Haydock (Committee reference 11/NW/0382) (29). In the current study (UKB project No. 55392), we analyzed participants with complete data on the Mental Health Questionnaire (29) that was used to assess PEs (N = 155,247; 57% female; mean age = 55.94 [SD = 7.74] years).

Psychotic Experiences

Guided by previous reports (13,16,27), a binary variable for any PEs (n = 7803) was defined as endorsement of any of the following 4 lifetime items: visual hallucination, auditory hallucination, reference delusion, and persecutory delusion. The specific wording of the items was as follows: ever seen an un-real vision, ever heard an un-real voice, ever believed in un-real communications or signs, and ever believed in an un-real conspiracy against self, respectively.

Correlates of Psychotic Experiences

For the current analyses, we included 148 variables (Supplement and Table e1) which were significantly associated with PEs in a previous exposome-wide association study (XWAS) after applying Bonferroni correction (13). These 148 exposures, consisting of 109 binary and 39 continuous variables, belong to 13 UKB categories including environmental, lifestyle, behavioral, and sociodemographic factors. Most exposures are associated with increased PEs, except for 26 exposures (such as vitamin D intake and general health rating) that were associated with decreased PEs.

In this study, we further dichotomized the 39 continuous exposures at the 75th percentile, assigning values of 1 and 0, consistent with our previous G×E interaction analyses (30,31). As previously suggested for additive interactions, we reverse coded the 26 negative correlates of PE, with 1 indicating high risk and 0 indicating low risk (32). This approach was used across all analyses to ensure comparable and consistent results (32). Therefore, the direction of effects of these 26 correlates on PEs differs from the previous study (Table e2).

PRS Estimation

Detailed methodology can be found in the Supplement. We calculated the PRS-SCZ for 151,627 participants who had available genetic and phenotypic information. We used summary statistics from the most recent GWAS of SCZ derived from individuals of European ancestry (21) to calculate PRS-SCZ. To estimate the PRSs, we used PRS-continuous shrinkage (33) (PRS-cs-auto) for the main analyses and PRSice2 (p value threshold = .05) (34) for sensitivity analyses. PRS-SCZ was dichotomized using quartile cutoff points based on the control distribution. Consistent with our previous work testing G×E interaction in psychosis (30), the highest quartile (PRS-SCZ > 75% of the control individuals) was considered the binary genetic risk state for SCZ for more interpretable and comparable testing of additive interactions. This cutoff was chosen based on previous research that demonstrated its effectiveness in identifying individuals at higher genetic risk for SCZ (30). Additionally, sensitivity analyses in previous studies have shown that additive interactions between PRS-SCZ and candidate exposures (e.g., regular cannabis use, childhood bullying, emotional abuse, sexual abuse, and emotional neglect) were consistent across different PRS-SCZ cut points (50% and 25%) (31). These findings support the rationale for the 75th percentile as an appropriate threshold for our analyses.

Statistical Analyses

Analyses were performed using R (version 4.0.4) (35) from November 1, 2023, to February 1, 2024. There were 3 sequential analytical steps (Figure e1). First, the correlations of PRS-SCZ with each of the 148 exposures were estimated using Pearson correlation coefficients. Second, we tested the main effects of PRS-SCZ on PEs using baseline logistic models with covariates, including sex, age, and the first 3 genetic principal components (PCs) (PEs ~ sex + age + PC1 + PC2 + PC3 + PRS-SCZ). In our previous work testing model specifications for adjusting for population stratification in PRS analyses in the UKB, we demonstrated that the first 3 PCs captured a substantial proportion of genetic variation related to population structure in the UKB cohort (Figure e2), which correlated well with geographic and ancestral

differences in the British population (36). Then, we added each of the 148 exposures into the PRS model (PEs ~ sex + age + PC1 + PC2 + PC3 + PRS-SCZ + exposure), using the interactionR package (37) to estimate G×E interactions. Third, the correlation of PRS-SCZ with each of the 148 exposures was estimated using Pearson correlations (37). Bonferroni correction was applied to adjust p values for multiple testing ($p < .05/148$). We also attempted to replicate previously demonstrated G×E interactions for birth weight and smoking behavior (26,27). Sensitivity analyses were conducted using PRSice-SCZ_{75} across all analytical steps.

Multiplicative and Additive Interaction

Interactions on the multiplicative scale (Ms) were used to assess whether the joint effect of PRS and exposure was greater than the product of their individual effects. For multiplicative interaction, we integrated a product term of the PRS-SCZ with each exposure on PEs in the logistic regression models. In addition to the Ms coefficients, corresponding p values and 95% CIs were reported.

Interactions on the additive scale were used to assess whether the joint effect of exposure and the PRS-SCZ was greater than the sum of their individual effects. Relative excess risk due to interaction (RERI), attributable proportion of interaction (AP), and the synergy index (SI), as well as corresponding p values and 95% CIs were utilized to perform effect modification analysis on the additive scale. We also estimated odds ratios (ORs), 95% CIs, and p values for each exposure and PRS strata to evaluate whether the effect of the exposure differed within the strata of PRS-SCZ. To estimate confidence intervals for the additive interactions, the simple asymptotic delta method (38) and the variance recovery (method of variance estimates recovery [MOVER]) method (39) were applied. As sensitivity analyses, we also estimated the confidence intervals of the interactions with the 39 continuous exposures and the continuous PRSs using the nonparametric bootstrapping method with 1000 bootstrap resampling (40).

Replication of Previous G×E Interactions

Recent studies have shown that G×E interactions in PEs related to birth weight and smoking behavior, using PRS-SCZ derived from PGC2 (Psychiatric Genomics Consortium freeze 2) (41) across different datasets. In addition to the exposome-wide interaction analyses, we attempted to replicate the genetic association findings using PRS-SCZ PGC3 (21).

RESULTS

Main Effects

In the baseline model (PEs ~ sex + age + PC1 + PC2 + PC3 + PRS-SCZ), PRS-cs-auto-SCZ_{75} significantly predicted PEs (OR, 1.14; 95% CI, 1.11–1.17; $p = 7.27 \times 10^{-24}$, R^2 = 0.21%). In the 148 conditional XWAS models (PEs ~ sex + age + PC1 + PC2 + PC3 + PRS-SCZ + exposure), when we added exposure to the logistic models, the significant effects of PRS-cs-auto-SCZ_{75} on PEs remained significant (ORs, 1.11–1.15; R^2 = 0.12–0.24%; p values = 6.6×10^{-13} to 1.1×10^{-26}) (Table e3). Under the condition of PRS-cs-auto-SCZ_{75}, all ORs of the 148 exposures remained significant (Figure e3). The sensitivity analyses with PRSice-SCZ_{75} confirmed these results (Table e3).

Multiplicative Scales

Among the 148 exposures, the only significant multiplicative interaction with PRS-SCZ was found for disability (other serious medical condition/disability diagnosed by the doctor, with the Ms = 1.23) (95% CI, 1.10–1.37; $p = 4.0 \times 10^{-4}$) (Table 1). For the exposures of visiting a psychiatrist for mental health, mental distress, vitamin D, and visiting a general practitioner (GP) for mental health, analyses indicated nominally statistically significant interactions (Table 2). In the sensitivity test using PRSice-SCZ_{75}, disability remained the top multiplicative interaction (Ms, 1.22; 95% CI, 1.092–1.37; $p = .0005$), but it was not statistically significant after Bonferroni correction. Furthermore, 3 nominally significant interactions remained: mental distress, visiting a psychiatrist for mental health, and vitamin D (Table e4).

Additive Interactions

Among the 148 variables, significant additive interactions were found for 7 exposures (disability, mental distress, sadness, help for mental distress, sleeping difficulties, visiting a GP for mental health, and visiting a psychiatrist for mental health) (Figure 1 and Table 3). Similar to the multiplicative interaction analyses, disability interacted with PRS-cs-auto-SCZ_{75} on an additive scale (RERI, 0.55; 95% CI, 0.32–0.77; SI, 0.22; 95% CI, 0.14–0.30; AP, 1.59; 95% CI, 1.30–1.91; all ps $< .05/148$)

Table 1. Interaction of Disability and PRS-cs-auto-SCZ_{75} on Psychotic Experiences

	Disability		
	No	Yes	Yes vs. No Within Strata of PRSice-SCZ
PRS-cs-auto-SCZ_{75} = 0	1 (Reference)	1.82 (1.72–1.94), $p < 10^{-5}$	1.82 (1.74–1.94), $p < 10^{-5}$
PRS-cs-auto-SCZ_{75} = 1	1.10 (1.04–1.17), $p = .023$	2.47 (2.27–2.69), $p < 10^{-5}$	2.24 (2.04–2.47), $p < 10^{-5}$
High PRS vs. Low PRS Within Strata of Disability	1.10 (1.04–1.17), $p = .023$	1.36 (1.23–1.49), $p < 10^{-5}$	
Multiplicative Scale	1.23 (1.10–1.38), $p = 3.3\times10^{-4}$		
Relative Excess Risk Due to Interaction	0.55 (delta: 0.32–0.77) (MOVER: 0.33–0.78), $p < 10^{-5}$		
Synergy Index	0.22 (delta: 0.14–0.30) (MOVER: 0.14–0.29), $p < 10^{-5}$		
Attributable Proportion	1.59 (delta: 1.32–1.91) (MOVER: 1.32–1.91), $p < 10^{-5}$		

Values are presented as OR (95% CI), p. Disability indicates other serious medical condition/disability diagnosed by a doctor.
MOVER, method of variance estimates recovery; PRS, polygenic risk score; PRS-cs-auto-SCZ, PRS for schizophrenia with continuous shrinkage.

Table 2. Significant Multiplicative Interactions of PRS-cs-auto-SCZ$_{75}$ and Exposures on Psychotic Experiences Were Identified Using an Exposome-Wide Interaction Study

Exposure	Category	Multiplicative Scale	95% CI	*p* Value
Disability[a]	Health and medical history[b]	1.23[b]	1.10–1.38[b]	4.0×10^{-4}[b]
Visit Psychiatrist for Mental Health[a]	Psychosocial factors	1.18	1.05–1.32	.006
Mental Distress[a]	Mental health	1.15	1.03–1.28	.013
Vitamin D[a]	Biological samples	0.94	0.89–0.99	.042
Visit GP for Mental Health	Psychosocial factors	1.12	1.00–1.23	.046

The full names of exposures are as follows: disability: other serious medical condition/disability diagnosed by a doctor; visit psychiatrist for mental health: seen a psychiatrist for nerves anxiety, tension, or depression; mental distress: ever experienced mental distress preventing usual activities; visit GP for mental health: seen doctor/GP for nerves, anxiety, tension, or depression.

GP, general practitioner; PRS-cs-auto-SCZ, polygenic risk score for schizophrenia with continuous shrinkage.

[a]Results that have been replicated in sensitivity tests using PRSice-SCZ$_{75}$.

[b]Identified as having significant multiplicative interaction with Bonferroni correction ($p < .05/148$).

(Table e1). The MOVER method identified similar confidence intervals (Table e5).

An additional 48 interactions were detected with nominal significance levels (Table e5 and Figure e4). Most of these exposures were from the UKB mental health (n = 25) and psychosocial factors (n = 15) categories, including cannabis use, self-harm, eating problems, sexual molestation as a child, and loneliness isolation. Furthermore, interactions were found with exposures from the following categories: health and medical history (n = 8; e.g., chest, dental, infirmity, hearing problem, and vitamin supplements), lifestyle and environment (n = 4; insomnia, diet change, milk types used, and hot drink temperature), physical measures (n = 2; fat mass and hand grip strength), and medical conditions (number of illnesses).

The sensitivity analyses using PRSice-SCZ$_{75}$ confirmed the 7 significant additive interactions. Furthermore, 39 of the 48 nominal significant additive interactions were confirmed (Table e5).

G×E Correlations

The correlation analyses revealed small (r range −0.021 to 0.058) but significant ($p < 2.02 \times 10^{-4}$) correlations between 102 exposures and PRS-cs-auto-SCZ$_{75}$ (Table e6). Ninety-four (r range −0.028 to 0.042) of these correlations remained significant using PRSice-SCZ$_{75}$ in sensitivity tests.

Focusing on the exposures with significant interactions with the PRS, disability and sleeping problems were not correlated with PRS-SCZ. Although the rest of the exposures that interacted with PRS-SCZ were positively correlated with PRS-cs-auto-SCZ$_{75}$, the magnitude of the correlations was very small (<0.04). These correlations were replicated in the sensitivity tests using PRSice-SCZ$_{75}$.

G×E Interaction With Birth Weight and Smoking

Birth weight was initially excluded from the previous XWAS due to a missing rate of >10%. Smoking status, pack years of smoking, and maternal smoking around the time of birth were also excluded due to collinearity, missingness, and being a follow-up variable, respectively. However, we extracted these variables to replicate previous findings and estimated the additive and multiplicative interactions with PRSice-SCZ$_{75}$ on PEs (Table e7 and Figure e5). Among these 4 variables, only a nominally significant additive interaction of smoking status with PRS-SCZ on PEs was found (RERI, 0.13; 95% CI, 0.014–0.266; p = .038).

DISCUSSION

To the best of our knowledge, this study represents the most extensive systematic inquiry into the exposome-wide G×E

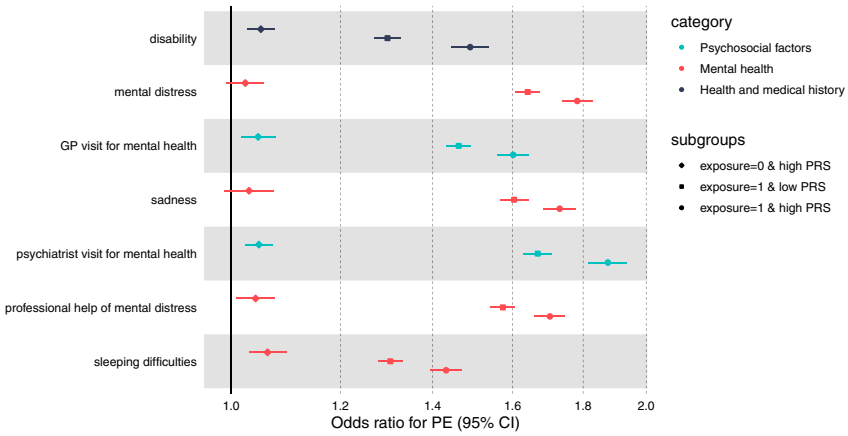

Figure 1. Odds ratios of psychotic experiences (PEs) in 55 exposures and polygenic risk score (PRS) subgroups. Fifty-five exposures are nominally significant in the additive interaction test. GP, general practitioner.

Table 3. Significant Additive Interaction Between PRS-cs-auto-SCZ$_{75}$ and Exposures on Psychotic Experiences Were Identified Using an Exposome-Wide Interaction Study

		RERI		AP		SI	
Exposure	Category	Estimate	*p* Value	Estimate	*p* Value	Estimate	*p* Value
Disability	Health and medical history	0.562	$<10^{-5}$	0.224	$<10^{-5}$	1.595	$<10^{-5}$
Mental Distress	Mental health	0.601	$<10^{-5}$	0.158	$<10^{-5}$	1.275	$<10^{-5}$
Sadness	Mental health	0.498	10^{-5}	0.141	$<10^{-5}$	1.244	$<10^{-5}$
Visit Psychiatrist for Mental Health	Psychosocial factors	0.894	10^{-5}	0.210	$<10^{-5}$	1.378	10^{-5}
Visit GP for Mental Health	Psychosocial factors	0.450	10^{-5}	0.152	$<10^{-5}$	1.298	10^{-5}
Help for Mental Distress	Mental health	0.465	3.0×10^{-4}	0.136	10^{-5}	1.239	3.0×10^{-5}
Sleeping Problem	Mental health	0.292	2.9×10^{-4}	0.127	1.4×10^{-4}	1.294	5.2×10^{-4}

The full names of exposures are as follows: disability: other serious medical condition/disability diagnosed by a doctor; mental distress: ever experienced mental distress preventing usual activities; sadness: ever had prolonged feelings of sadness or depression; visit psychiatrist for mental health: seen a psychiatrist for nerves, anxiety, tension, or depression; visit GP for mental health: seen doctor/GP for nerves, anxiety, tension, or depression; help for mental distress: ever sought or received professional help for mental distress; sleeping problem: trouble falling or staying asleep or sleeping too much. These variables are identified as having significant additive interaction with Bonferroni correction ($p < .05/148$). All the variable results have been replicated from sensitivity tests using PRSice-SCZ$_{75}$.

AP, attributable proportion; GP, general practitioner; PRS-cs-auto-SCZ, polygenic risk score for schizophrenia with continuous shrinkage; RERI, relative excess of risk due to interaction; SI, synergy index.

interaction of PEs conducted to date. It encompasses several sequential analytical steps, including an XWAS conditional on PRS-SCZ, an exposome-wide G×E interaction investigation, an exposome-wide G×E correlation estimation, and replication of previous G×E interaction analyses.

Our exposome-wide G×E interaction study identified significant multiplicative and additive interactions between disability and genetic risk of SCZ on PEs, as well as 7 significant additive interactions: 3 help- and treatment-seeking behaviors, mental distress, sadness, and sleep problems. In addition to the significant interactions, 4 multiplicative and 48 additive nominally significant interactions were identified, mainly in the domains of physical health outcomes, nonpsychotic disorders, mental distress, stress, trauma, help- and treatment-seeking behaviors, and sleep problems. Multiplicative interaction occurs when the combined effect of 2 factors differs from the product of their individual effects. This is commonly used in logistic regression models. In contrast, additive interaction occurs when the combined effect differs from the sum of individual effects. Overall, more significant additive interactions were detected than multiplicative interactions. Compared with multiplicative interaction tests, additive interaction tests may offer greater statistical power and yield more interpretable results from biomedical and epidemiological data (42).

Our study found that the impact of physical disability on PEs increased with higher PRS-SCZ, as revealed by both multiplicative and additive G×E interaction models. To the best of our knowledge, this is the first report indicating that the sensitivity to adverse physical conditions is moderated by PRS-SCZ. PE, an indicator of general health, has been associated with increased risk for disability across a broad range of functional domains, including social, role, cognitive functioning, mobility, and self-care (43). We showed that both conditional XWAS tests and XWIS models, which include a PRS-SCZ and G×E interactions, explained more variance in PEs than models in which only environmental factors were tested. This finding supports the idea that polygenic risk, poor physical health, and their combined influence are associated with subthreshold psychosis expression.

Additionally, we identified nominally significant additive interactions with milder physical health issues like chronic illness or recent fatigue, with smaller RERI (0.23, 0.17) and AP (0.09, 0.07) values than the Bonferroni-significant interaction of disability with more serious condition (RERI = 0.56, AP = 0.24), indicating stronger G×E interaction effects with severe health outcomes. Furthermore, G×E interactions have also been detected for other physical health outcomes, such as wheezing or whistling in the chest during the last year, chest pain, dental problems, taking other prescription medications, number of self-reported noncancer illnesses, and hearing problems. Our findings highlight G×E interactions of serious medical conditions or disabilities with genetic propensities for schizophrenia on PEs. This supports a conceptual framework in which underlying (nonspecific) immune dysfunction (e.g., autoantibodies, T cells, and B cells), with an estimated heritability of 30% (44), may serve as a foundational mechanism that leads to a broad spectrum of health outcomes, including psychosis, contingent on disease burden. Notably, the G×E interactions became stronger with increasing severity of the physical condition, suggesting a dose-response relationship in which increased disease burden may exacerbate PEs, akin to sickness behavior during illness (45,46). In this regard, immune system dysregulation and neuroinflammation may underlie behavioral and functional impairments (47). We acknowledge that some of the included variables may not strictly adhere to traditional definitions of environmental exposure. However, these were included to maintain consistency with the analytical pipeline applied in our previous work, an XWAS of PEs in the UKB, which aimed to eliminate data dredging and selective reporting that could be produced by preconceptions when determining what the environment is. However, this approach may introduce type II error due to the increased number of tests.

In the XWIS, 3 significant additive interactions were identified for treatment-seeking behavior linked to mental health problems: seeing a psychiatrist for nerves, anxiety, tension or depression; seen doctor/GP for nerves, anxiety, tension or depression; and ever sought or received professional help for mental distress. Consistent with our findings, this suggests

that targeting high PRS-SCZ and help-seeking individuals may aid in intervening in psychotic disorders. Furthermore, our findings identified suggestive interactions for well-known exposures such as cannabis use, self-harm, medical prescription, and having been sexually molested as a child, which is consistent with previous studies with independent samples (13,30).

According to the diathesis-stress theory, it is crucial to identify cumulative stressors that contribute to the manifestation of psychiatric symptoms in vulnerable populations such as people with PEs. The diathesis, or inherent vulnerabilities, are crucial for explaining why some individuals are more susceptible to developing psychiatric symptoms. Individuals with a high genetic predisposition to psychosis may experience cognitive deficits that could influence their response to environmental stressors and increase their likelihood of experiencing psychiatric symptoms (48). Cumulative stressors, such as ongoing life difficulties and acute stress events, can exacerbate vulnerability, potentially triggering adverse psychotic symptoms and increasing the need for intervention. It is critical to identify and manage cumulative stressors in genetically vulnerable populations, particularly populations with high genetic liability for SCZ. Overall, our results are consistent with the diathesis-stress model theory, suggesting that a combination of genetic predisposition and environmental stress contribute to the manifestation of PEs. Identifying high-risk individuals who are actively seeking help presents an opportunity for early intervention and better management of mental health concerns.

Several previous investigations have evaluated the interplay between PRS-SCZ and environmental variables underlying PEs. However, these studies have predominantly focused on a limited number of environmental factors such as stress (49), smoking behavior (27), and birth weight (26), which have not been verified in independent cohorts. In our study, we replicated previous findings with a suggestive interaction for stress ("felt very upset when reminded of a stressful experience in the past month and avoided activities" or "situations because of previous stressful experience in the past month") and smoking status.

Our findings highlight the complex interplay between genetic predisposition and environmental factors in the etiology of PEs. Previous exposome-wide analyses identified 148 exposures associated with PEs (13). The subsequent conditional cross-phenotype–wide association study (XWAS) reaffirmed that the relative impact of genetic factors on PEs (with only 0.2% of the variance explained by the PRS-SCZ) is notably lower than the impact of environmental exposures. Our results were consistent with the findings of a twin study suggesting that environmental factors may play a greater role than genetic factors in the etiology of PEs (20). However, it is crucial to emphasize that while environmental factors appear to have a larger impact, the role of genetic predisposition remains significant and cannot be overlooked. Even after adjusting for environmental exposures associated with PEs, we observed a persistent significant association between PRS-SCZ and PEs. This underscores that genetic risk for SCZ, although contributing a smaller proportion of variance, plays an essential role in the manifestation of PEs that is distinct from and complementary to the role played by environmental influences. Thus, our findings support a model in which both genetic and environmental factors contribute to the development of PEs, with environment explaining a slightly larger variance but genetic predisposition remaining an integral part of the equation. This emphasizes the need for a comprehensive approach to understanding and potentially intervening in the development of PEs that includes consideration of both genetic vulnerability and environmental exposures.

It is crucial to consider whether the PEs assessed in our older adult population (mean age >55 years) are related to, or on the same continuum as, PEs expressed by young adults who may be more prone to schizophrenia risk. Although our study provides valuable insights into the long-term manifestation of PEs, we acknowledge that the nature and implications of PEs may differ across age groups.

Our research has several strengths. First, the UKB's deep phenotyping and large sample size provide the requisite statistical robustness to discern subtle G×E interactions, even within complex multifactorial outcomes such as PEs. This capability enables the identification of interactions with heightened precision. Second, we used 2 widely recognized methods for PRS calculation: PRS-cs-auto and PRSice2. The PRS-cs-auto generation method allows for the efficient processing of vast amounts of genetic data and yields more statistically robust results, particularly in the context of larger sample sizes (33). Additionally, we utilized PRSice2 to generate PRS-SCZ, using a liberal p value threshold of .05 for sensitivity analyses, thereby enhancing the predictive power of genetic scores. Third, our study benefited from access to the most extensive GWAS summary statistics available to date (21). The variance in PEs explained by PRS-SCZ in our study (0.2%) is larger than another study that used summary statistics from PGC2 (27). Nevertheless, R^2 is relatively low, which suggests a small effect size. However, this should not be the sole criterion for assessing the importance of variables, especially in complex phenotypes like PEs. The biological plausibility and consistency with other findings should also be considered. Although our systematic approach was designed to mitigate biases and increase reproducibility, it was not without limitations. First, the sequential replication procedure and stringent multiple-testing correction might have inadvertently increased the likelihood of type II errors. Conversely, statistically significant but trivial effects can also emerge in analyses of large datasets. Second, we have not investigated any subtypes of PE; therefore, the contribution of genetic risk and exposures to specific types of PEs remains unknown. Secondly, our cross-sectional design limits our ability to make causal inferences. Some of the correlates of PE may be consequences rather than causes of PEs (for example, visiting a psychiatrist could be a result of experiencing PEs rather than a causal factor). We acknowledge the potential for reverse causality in our findings. Further studies of causal inference, such as Mendelian randomization, would be valuable in identifying potential causal mechanisms underlying PEs. Lastly, the proportion of variance in PEs explained by PRS-SCZ was minimal (<2%). Additional investigation is necessary to clarify the other genetic contributors (rare variants and copy number variants) to phenotypic variance. Our study focused on White British participants ages 48 to 63, which allows examination of cumulative environmental effects but may limit generalizability to

younger populations and other ethnic groups. Future research should investigate these G×E interactions across different ethnic and age groups, particularly in younger individuals during critical developmental periods. To enhance the reproducibility of our results, future studies could validate the identified exposures and their G×E interactions through hypothesis-driven research in independent cohorts.

Conclusions

The current study marks the first documentation of numerous exposures associated with PEs, after adjusting for polygenic risk for SCZ. These findings reveal preliminary evidence for G×E interaction in PEs and suggest that genetic vulnerability and exposures, specifically physical health conditions, may be intertwined in the pathway leading to psychosis. Our findings support the diathesis-stress theory and underscore the necessity of evaluating environmental and genetic influences in conjunction to elucidate biological mechanisms underlying psychosis.

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BDL and SG had full access to all the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. BDL and SG were responsible for concept and design. BDL was responsible for drafting of the manuscript and statistical analysis. BDL, L-KP, AA-M, BK, and SG were responsible for critical revision of the manuscript for important intellectual content. BPFR and SG were responsible for obtaining funding. SG was responsible for supervision. All authors participated in acquisition, analysis, or interpretation of data.

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All results and data generated and analyzed during this study are included in the Supplement. These supplemental materials provide the complete dataset necessary to interpret, verify, and extend the research presented in the article. For any additional information or access to specific datasets beyond what is provided in the Supplement, reasonable requests can be made to the corresponding author.

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