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Research paper

Interplay between polygenic risk for mood disorders and stressful life events in bipolar disorder

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ABSTRACT

Background: Although genetic and environmental factors are involved in the aetiology of bipolar disorder [BD], studies focused on their interplay are lacking. The current investigation examines interactions and correlations between polygenic risk scores [PRS] for BD and major depressive disorder [MDD] with stressful life events [SLEs] in liability for BD.

Methods: This study used data from 1715 participants (862 bipolar cases and 853 controls) taken from UK and Canadian samples. The List of Threatening Experiences Questionnaire recorded SLEs that occurred 6 months before interview for controls and 6 months prior to the first (Canadian sample) and worst (UK sample) depressive and manic episodes for bipolar cases. PRS-BD and PRS-MDD were calculated from the Psychiatric Genomics Consortium.

Results: For the worst depressive episode, the PRS-MDD was significantly correlated with total number of SLEs ($\beta = 0.13$, 95 % CI:0.04–0.22, $p = 0.003$) and dependent SLEs ($\beta = 0.09$, 95 % CI:0.02–0.16, $p = 0.007$). After correction for multiple testing nominally significant correlations were detected for PRS-BD with total number of SLEs ($\beta = 0.11$, 95 % CI:0.02–0.20, $p = 0.015$) and dependent SLEs ($\beta = 0.08$, 95 % CI:0.01–0.15, $p = 0.019$). Among bipolar cases, these associations were slightly stronger but were only of nominal significance for total number of SLEs (PRS-MDD: $\beta = 0.19$, 95 % CI:0.04–0.35, $p = 0.015$; PRS-BD: $\beta = 0.16$, 95 % CI:0.01–0.32, $p = 0.042$) and dependent SLEs (PRS-MDD: $\beta = 0.14$, 95 % CI:0.03–0.26, $p = 0.015$; PRS-BD: $\beta = 0.12$, 95 % CI:0.004–0.24, $p = 0.043$). No other significant gene-environment correlations or interactions were found.

Limitations: Use of a larger sample size would be beneficial.

Conclusions: The relationship between SLEs and genetic risk for mood disorders may be best explained through correlations rather than interactions.

1. Introduction

Bipolar disorder [BD] is a serious lifelong psychiatric illness characterised by extreme fluctuations in mood ranging from depression to mania (APA, 2013). BD is one of the major causes of disability globally (Ferrari et al., 2016), and is associated with a shorter life

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expectancy of up to 15 years (Hayes et al., 2017). Research is needed to fully uncover the aetiology of BD and identify predictors of its clinical expression to develop effective prevention and intervention strategies.

A wealth of research shows that experiencing stressful life events (e.g., bereavement and divorce) is associated with illness and episode onset as well as worsening of manic and depressive symptoms in BD (Hosang et al., 2012b, 2010a; Lex et al., 2017). Stressful life events [SLEs] can be categorised as independent (outside of one's control, e.g., bereavement) and dependent (influenced by one's behaviours and psychopathology, e.g., financial crisis) events. This categorisation helps to address whether SLEs are risk factors for (independent) or the consequence (dependent) of BD. Research in this area is inconsistent, with some studies reporting significant associations with independent events and symptoms of BD (Hosang et al., 2012b), while others only detect significant relationships between dependent but not independent SLEs (Hosang et al., 2012a). Stress vulnerability and generation factors may explain the disparate findings in the BD literature.

According to the stress diathesis model, the impact of stress on BD interacts or is moderated by an individual's vulnerability or 'diathesis' (Monroe and Simons, 1991). Various stress vulnerability factors in BD have been identified and include cognitive style and social support (Cohen et al., 2004; Reilly-Harrington et al., 1999). But genetic stress sensitivity in BD has received less research attention especially compared to other psychiatric illnesses, such as Major Depressive Disorder [MDD] (Uher, 2014), despite some promising findings.

Previous studies have found that the impact of SLEs in BD is significantly moderated by the Val^{66}Met variant in the Brain-derived neurotrophic factor [BDNF] gene and the Val^{158}Met polymorphism in the Catechol-*o*-methyltransferase [COMT] gene, for depressive rather than manic episodes (Hosang et al., 2017, 2010b). Given that advances in genetic methods have demonstrated that BD is likely to be polygenic (Mullins et al., 2021), there has been a move away from focusing on candidate genes in favour of utilising polygenic risk scores [PRS]. Analysing genetic risk factors in aggregate, as in PRS, may offer increased power to detect moderation of the effects of life stress on BD susceptibility. Several studies have found significant interactions between adverse childhood experiences (e.g., abuse and parental death) and PRS-BD on the clinical expression of BD (e.g., earlier age of onset and rapid cycling) (Aas et al., 2020; Park et al., 2020) and suicide attempts (Wilcox et al., 2017). But no BD studies exist which focus on the illness onset but rather the clinical course, SLEs and their interplay with PRS-BD.

The relationship between stress and genetic factors can also present as correlations whereby one's genetic predisposition may influence an individual's exposure to stress (Jaffee and Price, 2008). This could be via the exhibition of symptoms which leads to (dependent) SLEs, such as interpersonal conflict, job loss and financial crisis. Drawing on the MDD literature significant correlations between dependent SLEs and PRS-MDD have been observed (Mullins et al., 2016). In contrast, only a few studies have examined such gene-environment correlations in BD (Aas et al., 2020). But these studies have focused on adverse childhood experiences rather than SLEs (Aas et al., 2020), thus investigation of correlations between SLEs and PRS-BD is warranted.

Given that the PRS-MDD is associated with BD (Wray et al., 2018) and has been reported to significantly moderate the impact of life stress in depression (Mullins et al., 2016; Musliner et al., 2021; Peyrot et al., 2018), it would be prudent to also explore the possible relationship between life events and PRS-MDD in BD.

To our knowledge this is the first study to examine the interplay between polygenic risk for mood disorders and **SLEs** in BD, using two well characterised samples. The study will focus on SLEs reported prior to the first and worst mood episodes. Examining these index periods will provide information about gene-environment interplay with regards to illness onset (first mood episodes) and relapse (worst mood episodes). Specifically, this study has two objectives. Firstly, the interaction between SLEs for the first and worst mood episodes, the PRS-BD and PRS-MDD in BD will be investigated. It is hypothesised that the PRS for BD and MDD will significantly moderate the impact of SLEs on BD susceptibility, specifically for (first and worst) depressive rather than manic episodes, based on similar studies using candidate genes (Hosang et al., 2017, 2010b) and focused on childhood adversity (e.g., Aas et al., 2020). The second objective is to examine the correlation between SLEs for the first and worst mood episodes, the PRS-BD and PRS-MDD. It is anticipated that significant correlations between SLEs and the PRS-BD and PRS-MDD will be observed drawing on previous evidence focused on MDD (Mullins et al., 2016) as well as childhood adversity and BD (Aas et al., 2020).

2. Methods

2.1. Samples

The current investigation consists of 1715 participants (862 with BD and 853 healthy controls) taken from UK and Canadian samples (Gaysina et al., 2009; Zai et al., 2015). Participants were included in this study if necessary data was available for them (i.e., SLEs and PRS-BD and PRS-MDD). The Canadian sample consists of 384 individuals with BD (aged between 18 and 80) and 376 healthy controls (aged between 19 and 76) collected at the Centre for Addiction and Mental Health [CAMH]. The UK sample is comprised of 478 participants with BD (aged 19 and 90 years) and 477 healthy controls (aged 18–88 years) recruited from the Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK.

All participants are of European ancestry and aged 18 years and over. Participants were enrolled through advertisements in hospitals, clinics, family physicians' offices, or patient support groups between 2004 and 2007. The Schedules for Clinical Assessment in Neuropsychiatry [SCAN] (Wing et al., 1990) was used to confirm the patients' BD diagnoses according to DSM-IV and ICD-10 criteria which were the current diagnostic systems at the time. Individuals were excluded if they had a diagnosis of intravenous substance dependence, reported intravenous substance use, mood-incongruent psychotic symptoms, and/or manic episodes related to substance abuse, substance dependence, medication, or medical illness. Healthy controls were included if they had no (self-reported) personal or family history of any psychiatric disorder. The studies were carried out in accordance with the latest version of the Declaration of Helsinki in 1975 (revised in 2008) and all participants provided written informed consent. Ethical approvals were obtained from the Joint South London and Maudsley, and Institute of Psychiatry Research Ethics Committee approved for the UK sample (ref: 187/02). The Canadian study received ethical approval from CAMH Research Ethics Board (ref: 049/2004).

2.2. Measures

The List of Threatening Experiences Questionnaire (Brugha et al., 1985) was used to record the experience of 11 different SLEs experienced 6 months prior to the index periods. For BD cases, the index periods were self-identified first (Canadian sample) and worst (UK samples) mood episodes. These episodes occurred between 10 and 20 years prior to interview, for the worst and first episodes respectively. Controls reported events that occurred prior to their interview. This questionnaire was selected for its brevity for use in large genetic case-control studies and because it is designed to capture events which carry significant long-term threat and particular pertinence for mood disorders (Brugha et al., 1985). High test-retest reliability and concurrent validity have been reported for this instrument (Brugha and Cragg, 1990). For instance, research shows that the List of Threatening Experiences Questionnaire successfully records 82.5 % of the events assessed in more extensive interviews (Brugha and Cragg, 1990). Based on previous research the 11 events were divided into two categories: dependent events (items 5–11: separation due to marital difficulties or break

up of a steady relationship; serious problem with a close friend, neighbour or relative; job loss; seeking work without success for >1 month; major financial crisis; problems with the police involving a court appearance; valued item lost or stolen) that were related to an individual's behaviour and decisions. The second category is independent events (items 1–4: serious illness, injury or assault; serious illness, injury or assault of close relative; death of a spouse or first-degree relative; death of a close family friend or other relative) these occur outside of the control of the individual.

2.3. Genotyping

Genotyping of both samples was carried out on the Illumina Sentrix Human Hap550 Beadchip (Illumina Inc., San Diego, CA, USA) mostly at Illumina Inc. (San Diego, CA, USA), with 290 Canadian participants genotyped at the Genome Quebec facility (Montreal, Quebec, Canada).

We performed genotype quality control for each sample separately using PLINK (Purcell et al., 2007) and R (Team, 2013). Briefly, participants were excluded if their reported sex did not match their genotype sex, had outlying levels of heterozygosity, or were related to any other participants. SNPs with minor allele frequency of <1 %, >1 % missing genotypes, or genotypes deviating significantly from Hardy-Weinberg Equilibrium (p < 1e-6) were excluded. We performed an analysis of population structure via principal component analysis of the genotypes to retain the European cluster. We performed principal component analysis again after quality control procedures to remove population outliers, and we used the first ten principal components (PC1 to PC10), as covariates in the analyses. After quality control, we inputted 489,932 SNPs for 384 BD cases and 377 controls for the Canadian sample, and 484,394 SNPs for 447 BD cases and 431 controls for the UK sample for whole-genome imputation.

We performed whole-genome imputation on the Michigan Imputation Server (Minimac4; CAMH Specialized Computing Cluster) with 1000 Genomes Phase 3 data as reference, haplotype phasing using Eagle v2.4, and minimum R-squared threshold of 0.3 (Das et al., 2016), with an additional filtering for SNPs with R-Squared value of at least 0.9. Whole-genome imputation and quality control yielded 6,409,831 SNPs for the 761 CAN participants, and 6,502,266 SNPs for the 869 UK participants. PRS-BD and PRS-MDD were calculated for each individual using the continuous shrinkage approach [PRS-cs-auto using default settings] (Ge et al., 2019). PRS were drawn from publicly available genome-wide association study summary statistics for BD (Mullins et al., 2021) and MDD (Wray et al., 2018). To validate the PRS method, we also calculated PRS-BD and PRS-MDD from PRSice2 (Choi and O'Reilly, 2019) using best-performing p-value thresholds of $p = 0.1$ and $p = 0.05$ for BD (Mullins et al., 2021) and MDD (Wray et al., 2018).

2.4. Data analysis

We performed statistical analyses in STATA version 15. First, we tested the effect of PRS-BD or PRS-MDD on affected status of BD, including sex, age, PC1 to PC10, and the interaction terms for PRS with PC1 to PC10 as covariates. Next, we examined the impact of the number of the overall, dependent, and independent SLEs on BD affected status, including sex, age, PC1 to PC10 and the interaction terms for the SLEs with PC1 to PC10 as covariates. Gene-environment correlation analyses were tested by regressing SLEs against PRS-MDD and PRS-BD, controlling for sex, age, PC1 to PC10. Regression models were run separately for the first and worst episodes using the entire sample. The models were also repeated separately for cases and controls. This was to ascertain whether any detected gene-environment correlations were specific to any one group (cases or controls), this approach has been used previously (Mullins et al., 2016). Gene-environment interactions were tested using two models. Multiplicative gene-environment interaction models test whether the combined effect of the PRS and SLEs is different from the product of their individual effects. These were tested using logistic regressions which include the main effects of the PRS-BD or PRS-MDD, SLEs (total, dependent or independent) the PRS × SLEs interaction, controlling for sex, age, PC1 to PC10, interaction terms for PRS with PC1 to PC10, as well as interaction terms for SLEs with PC1 to PC10 (Keller, 2014). The additive gene-environment interaction model tests whether the combined effect of the PRS and SLEs differ from the sum of their individual effects. It has been argued that departure from additivity may better reflect biological interactions (Karg and Sen, 2012). Additive gene-environment interactions were tested using linear regressions on BD case/control status with the predictor variable being the interaction term using the same covariates outlined for the multiplicative models (above), in line with previous studies (Mullins et al., 2016).

Our total sample size of 1715 has enough power to detect ORs for the effects of PRS-BD or PRS-MDD (OR = 1.46), 1+ SLEs (OR = 1.34) on BD. The study had >80 % power to detect an interaction between PRS and SLEs with an OR of 1.81 (QUANTO) (Gauderman and Morrison, 2006). The Bonferroni corrected significance level was set at $p < 0.008$ to account for 6 test for each mood episode (depressive or manic), type of life event (total, dependent and independent) and PRS (PRS-BD and PRS-MDD).

3. Results

3.1. Sample characteristics

Data from two case-control genetic association studies were analysed in this investigation, one from Canada and the other from the UK (see Table 1 for sample description). No gender differences were detected between cases and controls in the Canadian ($\chi^2(1) = 0.48$, $p > 0.05$) or UK ($\chi^2(1) = 2.04$, $p > 0.05$) samples. But significant age differences were observed. In the Canadian sample, bipolar cases were significantly younger than the controls ($t(606) = 24.88$, $p < 0.001$). The opposite was found for the UK study, where participants with BD were significantly older than the controls ($t(819) = 5.44$, $p < 0.001$). Bipolar cases reported significantly more SLEs prior to their depressive and manic episodes compared to controls for the period before their interview (Table 1). These findings were observed in both samples. Although only a nominally significant difference was found for independent SLEs reported before the worst manic episode ($t(819) = 1.70$, $p = 0.09$).

Using the PRS-cs approach BD case status was significantly associated with the PRS-BD (odds ratio [OR] = 1.28, 95 % Confidence Intervals [CI] 1.10–1.49, $p = 0.001$) and PRS-MDD (OR = 1.25, 95 % CI 1.08–1.44, $p = 0.003$) in the UK sample. For the Canadian sample neither of the PRS were significantly associated with case status when the PRS continuous shrinkage approach was employed (PRS-BD: OR = 0.94, 95 % CI 0.76–1.17, $p > 0.05$; PRS-MDD: OR = 0.95, 95 % CI 0.77–1.18, $p > 0.05$). However, when using the PRS P-value threshold associated with the best explained liability for disease from the discovery GWAS datasets (PRS-BD: $P = 0.1$ (Mullins et al., 2021); PRS-MDD: $P = 0.05$ (Wray et al., 2018)), a significant association was detected between BD case-status and PRS-BD (OR = 1.42, 95 % CI 1.14–1.77, $p = 0.002$) but not PRS-MDD (OR = 0.92, 95 % CI 0.75–1.15, $p > 0.05$). The PRS-cs approach was used in the remaining analyses.

3.2. Gene-environment correlations: SLEs, BD and MDD PRS

In the Canadian sample, no significant correlations between SLEs reported prior to the first mood episodes and PRS-BD or PRS-MDD were detected (Table 2). In the UK sample some gene-environment correlations were observed for the worst depressive but not manic episodes. Specifically, PRS-MDD was significantly associated with the total number of SLEs (ß = 0.13, 95 % CI:0.04–0.22, $p = 0.003$) and dependent SLEs (ß = 0.09, 95 % CI:0.02–0.16, $p = 0.007$) reported before the worst depressive episode. But nominally significant correlations were found for PRS-BD with the total number of SLES (ß = 0.11, 95 % CI:0.02–0.20, $p = 0.015$), and dependent SLEs (ß = 0.08, 95 % CI:0.01–0.15, p =

Table 1
Sample characteristics.

Sample	Canada ($N = 760$)				UK ($N = 821$)			
Affected status	Cases $n = 383$ n (%)	Controls[a] $n = 377$ n (%)	Statistic (df)	P-value	Cases $n = 396$ n (%)	Controls[a] $n = 425$ n (%)	Statistic	P-value
Female	234 (61)	221 (59)	χ^2 (1) = 0.48	0.49	264 (67)	263 (62)	χ^2 (1) = 2.04	0.15
Mean age in years (SD)[b]	23.2 (10.3)	44.3 (13.0)	t(606) = 24.88	<0.001	37.0 (11.4)	32.4 (13.1)	t(819) = 5.44	<0.001
Number of stressful life events reported before								
Depressive episode# (mean, SD)	1.75 (1.81)	1.03 (1.23)	t(606) = 5.85	<0.001	1.34 (1.50)	0.77 (0.98)	t(819) = 6.47	0.001
Manic episode (mean, SD)	1.88 (1.84)	1.03 (1.23)	t(527) = 6.21	<0.001	1.29 (1.41)	0.77 (0.98)	t(819) = 6.12	<0.001
Number of **dependent** life events reported before								
Depressive episode (mean, SD)	1.01 (1.24)	0.60 (0.95)	t(606) = 4.65	<0.001	0.84 (1.14)	0.40 (0.68)	t(819) = 6.78	<0.001
Manic episode# (mean, SD)	1.12 (1.29)	0.60 (0.95)	t(527) = 5.13	<0.001	0.84 (1.10)	0.40 (0.68)	t(819) = 6.94	<0.001
Number of **independent** stressful life events reported before								
Depressive episode (mean, SD)	0.74 (0.97)	0.43 (0.68)	t(606) = 4.57	<0.001	0.50 (0.76)	0.37 (0.59)	t(819) = 2.70	0.007
Manic episode# (mean, SD)	0.76 (1.01)	0.43 (0.68)	t(527) = 4.39	<0.001	0.44 (0.67)	0.37 (0.59)	t(819) = 1.70	0.09

Abbreviations: OR, odds ratio; CI confidence intervals; SD, standard deviation; %, percentage.
[a] Numbers of total, dependent, and independent stressful life events before depressive episodes are the same as those before manic episodes for controls for both the Canada and UK samples.
[b] Age at onset for Canadian sample, age at worst manic episode for UK sample, and age at interview for Canadian and UK controls.

Table 2
Gene-environment correlations between stressful life events and the polygenic risk scores for bipolar disorder and major depressive disorder presented separately for depressive and manic episodes and by cohort.

	Canada			UK		
	ß	95 % CI	P-value	ß	95 % CI	P-value
Depressive episode	All	($N = 608$)		All	(N = 821)	
All event: PRS-BD	0.04	−0.09-0.16	0.541	0.11	0.02–0.20	**0.015***
All event: PRS-MDD	0.02	−0.11-0.14	0.789	0.13	0.04–0.22	**0.003*****
Dependent event: PRS-BD	0.06	−0.03-0.15	0.195	0.08	0.01–0.15	**0.019***
Dependent event: PRS-MDD	0.04	−0.05-0.13	0.358	0.09	0.02–0.16	**0.007*****
Independent event: PRS-BD	−0.02	−0.09-0.05	0.547	0.03	−0.01-0.08	0.179
Independent event: PRS-MDD	−0.02	−0.09-0.04	0.460	0.04	−0.004-0.09	0.072
	Cases	(***N*** = 231)		Cases	(N = 396)	
All event: PRS-BD	−0.13	−0.39-0.13	0.331	0.16	0.01–0.32	**0.042***
All event: PRS-MDD	−0.16	−0.43-0.11	0.253	0.19	0.04–0.35	**0.015***
Dependent event: PRS-BD	−0.02	−0.20-0.16	0.825	0.12	0.004–0.24	**0.043***
Dependent event: PRS-MDD	−0.04	−0.23-0.14	0.648	0.14	0.03–0.26	**0.015***
Independent event: PRS-BD	−0.11	−0.25-0.03	0.121	0.04	−0.04-0.12	0.320
Independent event: PRS-MDD	−0.11	−0.26 − 0.03	0.118	0.05	-0.03-0.13	0.227
Manic episode	All	(***N*** = 529)		All	(N = 821)	
All event: PRS-BD	0.02	−0.10-0.15	0.726	−0.003	−0.09-0.08	0.955
All event: PRS-MDD	0.01	−0.11-0.14	0.869	0.01	−0.07-0.10	0.784
Dependent event: PRS-BD	0.04	−0.06-0.13	0.440	−0.006	−0.07-0.06	0.867
Dependent event: PRS-MDD	0.02	−0.07-0.11	0.631	−0.002	−0.07-0.06	0.954
Independent event: PRS-BD	−0.01	−0.08-0.05	0.692	0.003	−0.04-0.05	0.891
Independent event: PRS-MDD	−0.01	−0.08-0.06	0.731	0.01	−0.03-0.06	0.535
	Cases	(***N*** = 152)		Cases	(N = 396)	
All event: PRS-BD	−0.09	−0.40-0.23	0.587	−0.09	−0.23-0.06	0.239
All event: PRS-MDD	−0.09	−0.40-0.22	0.578	−0.07	−0.21-0.08	0.370
Dependent event: PRS-BD	−0.002	−0.22-0.21	0.983	−0.07	−0.18-0.05	0.241
Dependent event: PRS-MDD	−0.03	−0.24-0.19	0.799	−0.06	−0.17-0.06	0.333
Independent event: PRS-BD	−0.08	−0.25-0.08	0.328	−0.02	−0.09-0.05	0.592
Independent event: PRS-MDD	−0.06	−0.23-0.11	0.483	−0.01	−0.08-0.06	0.773
	Controls	(N = 377)		Controls	(N = 425)	
All event: PRS-BD	0.11	−0.02-0.24	0.089	0.03	−0.06-0.13	0.458
All event: PRS-MDD	0.09	−0.04-0.21	0.173	0.04	−0.05-0.14	0.349
Dependent event: PRS-BD	0.09	−0.01-0.19	0.068	0.02	−0.05-0.08	0.630
Dependent event: PRS-MDD	0.08	−0.02-0.17	0.112	0.01	−0.05-0.08	0.697
Independent event: PRS-BD	0.02	−0.05-0.09	0.591	0.02	−0.04-0.08	0.503
Independent event: PRS-MDD	0.009	−0.06-0.08	0.803	0.03	−0.02-0.09	0.273

Abbreviations: CI confidence intervals; %, percentage, PRS-BD, polygenic risk score for bipolar disorder; PRS-MDD, polygenic risk score for major depressive disorder.
***p<0.008 Bonferonni corrected significance level.
**p<0.01.
*p<0.05.

0.019) after correction for multiple testing (Table 2).

These gene-environment correlations were slightly stronger among bipolar cases when compared to the results for the whole sample and controls for PRS-MDD (total SLEs: β = 0.19, 95 % CI:0.04–0.35, p = 0.015; dependent SLEs: β = 0.14, 95 % CI:0.03–0.26, p = 0.015) and PRS-BD (total SLEs: β = 0.16, 95 % CI:0.01–0.32, $p = 0.042$; dependent SLEs: β = 0.12, 95 % CI:0.004–0.24, $p = 0.043$) however they were considered of nominal significance after correction for multiple testing. No significant correlations were detected for controls.

3.3. Gene-environment interactions between SLEs, BD and MDD PRS

Gene-environment interaction analyses did not yield statistically significant findings for either sample under multiplicative (Tables 3) or additive models (Table 4) for either PRS (BD or MDD).

4. Discussion

This is the first BD study, to our knowledge, which has investigated the relationship between SLEs and polygenic risk for BD and MDD. Our results uncover significant gene-environment correlations between the PRS-MDD and the *total number of* as well as *dependent* SLEs for the worst but not first episodes of depression. Nominally significant correlations between PRS-BD and total number of and dependent SLEs were found after correction for multiple testing. No associations or interactions were found for the first or worst manic episodes.

When the sample was stratified by case/control status, nominally significant results were found for the BD cases, but not for controls. Although the positive associations were stronger for the cases (range: ß = 0.05 to ß = 0.19) compared to the results for the whole sample (range: ß = 0.03 to ß = 0.13). Suggesting the significant results may be driven by the correlations observed in the BD sample, and lack of significance maybe due to sample size/power. We found no evidence for significant gene-environment interactions under multiplicative or additive models.

These findings provide a novel contribution to the small but growing BD literature concerning the relationships between life stress and polygenic risk for mood disorders. For instance, significant interactions and correlations between PRS-BD and childhood trauma on the course of BD have been reported previously (Aas et al., 2020; Park et al., 2020). We extend this work by focusing on a different type of adversity–SLEs and include the PRS-MDD. Our novel results show that individuals at increased genetic risk for BD and MDD report more SLEs prior to the worst depressive but not manic episode, although only the latter remained significant after correction for multiple testing. Interestingly our results indicate that this correlation becomes apparent during the course rather than onset of the illness, may be when symptoms are more common. It would be helpful for future gene-environment correlation studies to focus on SLE occurrence after episode onset to determine whether symptoms result in dependent life events.

It is important to acknowledge that SLEs are influenced by genetic factors and therefore cannot be considered purely environmental in nature. For instance, heritability estimates of between 20 % to 50 % have been reported for SLEs (Billig et al., 1996; Shakoor et al., 2018; Thapar et al., 1998), with up to 30 % of their variance accounted for by common genetic variants captured using single nucleotide polymorphisms (Power et al., 2013). Our results add to this literature by indicating that SLEs are associated with genetic liability of BD and MDD.

There are three main types of gene-environment correlations, two of which are relevant to this study. Evocative or reactive gene-environment correlation refers to the association between one's genetically influenced behaviour (or symptoms) and the reaction of others to this behaviour (Zwicker et al., 2018). It is possible that an individual at increased genetic risk for BD and MDD may experience irritability (depressive and manic symptom) which may trigger or provoke conflicts with loved ones (a SLE) (Zwicker et al., 2018) leading to a relapse.

Active or selective gene-environment correlation refers to the association between one's genetic propensity and the environment they select (Zwicker et al., 2018). Research shows that PRS-BD and MDD are associated with substance use disorders (Hodgson et al., 2020; Reginsson et al., 2018) thus individuals with high PRS scores for BD and MDD may be more likely to seek out risky environments and peer groups. Together these circumstances could result in problems with the police or law (dependent SLE) as well as leading to the onset of a mood episode. The type of gene-environment correlation detected in the current investigation is unclear and should be clarified with further research.

Given the significant correlations between childhood trauma and PRS-BD, it would be useful for future studies to consider the relationship between multiple environmental factors (e.g., childhood trauma and SLEs) and PRS-BD as well as PRS-MDD in combination to provide a more comprehensive picture.

This was also the first study to explore the interaction between SLEs, PRS-BD and PRS-MDD in BD. Candidate gene studies have previously shown that the impact of life events are significantly moderated by the *BDNF* Val^{66}Met (Hosang et al., 2010b) and *COMT* Val^{158}Met (Hosang et al., 2017) polymorphisms for depressive rather than manic episodes in BD. In contrast, we found no evidence of significant interactions between PRS-BD or PRS-MDD and SLEs in BD. One explanation of these findings is that the genetic moderation of the impact of SLEs on BD may

Table 3
Multiplicative interaction between polygenic risk scores for bipolar disorder and major depressive disorder with stressful life events experienced before depressive and manic episodes for bipolar cases and before interview for controls, presented separately for Canada and UK samples.

PRS-BD	Canada				UK			
	OR	95 % CI	RSq	P-value	OR	95 % CI	RSq	P-value
Depressive episode	(N = 608)				(N = 821)			
All event × PRS-BD	0.92	0.74–1.14	0.001	0.421	1.11	0.96–1.29	0.003	0.164
Dependent event × PRS-BD	0.85	0.63–1.15	0.001	0.287	1.14	0.93–1.39	0.002	0.220
Independent event × PRS-BD	0.88	0.62–1.26	0.001	0.492	1.15	0.88–1.49	0.002	0.309
Manic episode	(N = 529)				(N = 821)			
All event × PRS-BD	1.01	0.81–1.25	<0.001	0.927	0.93	0.80–1.08	0.001	0.337
Dependent event × PRS-BD	1.19	0.88–1.60	0.002	0.265	0.92	0.75–1.13	0.001	0.421
Independent event × PRS-BD	0.73	0.48–1.11	0.003	0.145	0.92	0.71–1.20	<0.001	0.538

PRS-MDD	Canada				UK			
	OR	95 % CI	RSq	P	OR	95 % CI	RSq	P
Depressive episode	(N = 608)				(N = 821)			
All event × PRS-MDD	0.91	0.73–1.12	0.001	0.369	1.11	0.95–1.29	0.003	0.184
Dependent event × PRS-MDD	0.88	0.66–1.19	0.001	0.411	1.15	0.94–1.40	0.002	0.184
Independent event × PRS-MDD	0.84	0.58–1.22	0.001	0.360	1.11	0.85–1.45	0.001	0.435
Manic episode	(N = 529)					(N = 821)		
All event × PRS-MDD	0.98	0.80–1.20	<0.001	0.826	0.93	0.81–1.08	0.001	0.362
Dependent event × PRS-MDD	1.09	0.82–1.45	0.001	0.570	0.93	0.76–1.14	0.001	0.494
Independent event × PRS-MDD	0.74	0.49–1.13	0.003	0.161	0.92	0.71–1.20	<0.001	0.546

Abbreviations: OR, odds ratio; CI confidence intervals; %, percentage; PRS-BD, polygenic risk score for bipolar disorder; PRS-MDD, polygenic risk score for major depressive disorder.

Table 4
Additive interaction between polygenic risk scores for bipolar disorder and major depressive disorder with stressful life events experienced before depressive and manic episodes for bipolar cases and before interview for controls, presented separately for Canada and UK samples.

PRS-BD	Canada				UK			
	β	95 % CI	RSq	P-value	β	95 % CI	RSq	P-value
Depressive episode		(N = 608)				(N = 821)		
All event × PRS-BD	−0.01	−0.03 − 0.01	<0.001	0.262	0.01	-0.01-0.04	<0.001	0.302
Dependent event × PRS-BD	−0.02	−0.05-0.01	<0.001	0.187	0.02	−0.02-0.06	<0.001	0.377
Independent event × PRS-BD	−0.02	−0.06-0.02	<0.001	0.384	0.02	−0.03-0.08	<0.001	0.412
Manic episode		(N = 529)				(N = 821)		
All event × PRS-BD	−0.003	−0.03 − 0.02	<0.001	0.797	-0.02	−0.04-0.01	<0.001	0.301
Dependent event × PRS-BD	0.004	−0.03-0.04	<0.001	0.806	−0.02	−0.06-0.02	<0.001	0.300
Independent event × PRS-BD	−0.03	−0.07-0.01	0.002	0.151	−0.02	−0.08-0.03	<0.001	0.428

PRS-MDD	Canada				UK			
	β	95 % CI	RSq	P-value	β	95 % CI	RSq	P-value
Depressive episode	(N = 608)				(N = 821)			
All event × PRS-MDD	−0.01	−0.04 − 0.01	<0.001	0.192	0.02	-0.01-0.04	0.001	0.293
Dependent event × PRS-MDD	−0.02	−0.05-0.01	0.001	0.239	0.02	−0.02-0.06	<0.001	0.289
Independent event × PRS-MDD	−0.02	−0.06-0.02	<0.001	0.262	0.02	−0.04-0.07	<0.001	0.549
Manic episode	(N = 529)				(N = 821)			
All event × PRS-MDD	−0.01	−0.03-0.02	<0.001	0.587	−0.01	−0.04-0.01	<0.001	0.301
Dependent event × PRS-MDD	−0.002	−0.03-0.03	<0.001	0.914	−0.02	−0.06-0.02	<0.001	0.378
Independent event × PRS-MDD	−0.03	−0.08-0.01	0.001	0.156	−0.02	−0.08-0.03	<0.001	0.434

Abbreviations: CI confidence intervals; %, percentage, PRS-BD, polygenic risk score for bipolar disorder; PRS-MDD, polygenic risk score for major depressive disorder.

be best captured as genetic sensitivity to stress rather than genetic risk for BD or MDD. Several studies have developed PRS for stress or environmental sensitivity. For instance, one study found that the PRS-stress sensitivity significantly moderated the impact of SLEs on depression (Davidson et al., 2021). It would be fruitful for future BD studies to explore the interplay between life events and PRS-stress sensitivity.

Our findings have important research and clinical implications, for instance they provide support for the relevance of the stress generation hypothesis to BD (Bender et al., 2010). According to this hypothesis symptoms of depression and mania influence the generation of subsequent dependent life events (e.g., irritability leading to interpersonal conflict) (Bender et al., 2010). In turn, such events may exacerbate symptoms potentially triggering a clinical episode of depression or mania (Bender et al., 2010). We found that individuals with higher genetic risk for MDD and BD experienced more SLEs. When analyses were stratified by BD/control status, the associations were stronger although only nominally significant for those with BD. The clinical implications of these findings are two-fold. First, that the reporting of SLEs may highlight a period when an individual is at increased risk of developing BD or relapse among those with the disorder, through the presence of symptoms and experience of stress related to the occurrence of SLEs (Bender et al., 2010). Second, intervention and management strategies focusing on monitoring and managing *symptoms* to prevent the occurrence of dependent life events may be effective in mitigating the risk of full-blown episodes of depression and mania.

4.1. Strengths and limitations

There are a number of methodological strengths of this study including the use of well-characterised BD samples and psychometrically robust self-report SLEs questionnaire, however there are several limitations which should be considered when interpreting our findings. Firstly, SLEs were assessed using a self-report questionnaire which has several shortcomings. For instance, the instrument used here (i.e., List of Threatening Experiences Questionnaire), only covers 11 different types of events so it is possible that important stressful circumstances are not covered, and information is missed. However, the instrument was developed to cover those events which are known to be most relevant to mood disorders based on gold standard interview studies (Brugha and Cragg, 1990). A crucial aspect of the life events assessment is the independence of each event, which can only really be established by collecting circumstantial information. These limitations could be addressed by using life event interviews, enquiring about a wide range of life events and circumstantial information considered. However, such interviews are time and labour intensive and therefore expensive, especially when employed in large samples needed to investigate gene-environment interactions and correlations. It would be useful for the findings from this study to be replicated using life event interviews.

Secondly, the index periods for reporting SLEs for cases and controls in this study are not the most comparable and may impact the results. Controls were asked to report SLEs experienced 6 months before their interview, whereas BD cases recorded those events experienced 6 months prior to their first and worst episodes. Given SLEs are known to cluster before mood episodes (Lex et al., 2017), case-control SLE differences are not surprising and may be magnified here. Future studies would benefit from using index periods for cases and controls which are similar to surmount these challenges. Another limitation is the sample size. Although power calculations reveal our sample is sufficient to detect both gene-environment interactions and correlations it would be useful if the results could be replicated in larger studies to ensure confidence in the results.

4.2. Conclusion

This is the first BD study to examine the relationships between SLEs and polygenic risk for BD and MDD. This investigation found a significant correlation between PRS-MDD with SLEs for the worst but not the first depressive episodes. For PRS-BD nominally significant correlations with life events were detected. We found no evidence of interactions between SLEs and PRS-BD or PRS-MDD.

CRediT authorship contribution statement

Georgina M. Hosang: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Sania Shakoor:** Writing – review & editing. **Nicole King:** Data curation, Writing – review & editing. **Marcos Sanches:** Formal analysis, Writing – review & editing. **John B. Vincent:** Data curation, Funding acquisition, Methodology,

Project administration, Writing – review & editing. **James L. Kennedy:** Data curation, Funding acquisition, Methodology, Project administration, Writing – review & editing. **Peter McGuffin:** Data curation, Funding acquisition, Methodology, Project administration, Writing – review & editing. **Robert Keers:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **Clement C. Zai:** Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interests.

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