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Research paper

Multiple psychiatric polygenic risk scores predict associations between childhood adversity and bipolar disorder

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ABSTRACT

Background: It remains unclear how adverse childhood experiences (ACE) and increased genetic risk for bipolar disorder (BD) interact to influence BD symptom outcomes. Here we calculated multiple psychiatric polygenic risk scores (PRS) and used the measures of ACE to understand these gene-environment interactions.
Method: 885 BD subjects were included for analyses. BD, ADHD, MDD and SCZ PRSs were calculated using the PRS-CS-auto method. ACEs were evaluated using the Children Life Event Questionnaire (CLEQ). Participants were divided into groups based on the presence of ACE and the total number of ACEs. The associations between total ACE number, PRSs and their interactions were evaluated using multiple linear and logistic regressions. Secondary analyses were performed to evaluate the influence of ACE and PRS on sub-phenotypes of BD.
Results: The number of ACEs increased with the ADHD PRS. BD participants who had ACEs showed an earlier age of BD onset and higher odds of having rapid cycling. Increased BD PRS was associated with increased odds of developing psychotic symptoms. Higher ADHD PRS was associated with increased odds of having rapid cycling. No prediction effect was observed from MDD and SCZ PRS. And, we found no significant interaction between ACE numbers and any of the PRSs in predicting any selected BD sub-phenotypes.
Limitations: The study was limited by sample size, ACE definition, and cross-sectional data collection method.
Conclusions: The findings consolidate the importance of considering multiple psychiatric PRSs in predicting symptom outcomes among BD patients.

1. Introduction

Bipolar disorder (BD) is a severe and often chronic psychiatric disorder characterised by irregular episodes of elevated, depressed, or mixed mood states (American Psychiatric Association, 2013). BD was estimated to affect the 40–50 million global population, with a constant prevalence of around 2 % (Merikangas et al., 2011). Population increase and ageing have accounted for the growth of total BD cases (Ferrari et al., 2016).

BD is recognised as a complex psychiatric disorder because of its variable clinical presentation. The first episode of mania or depression of BD commonly occurs between the ages of 18 and 24 (McMahon et al., 1994). However, early onset before age 18 is not rare and such cases are often associated with more severe or complex BD phenotypes, such as increased comorbidity and delayed treatment response (Joslyn et al., 2016). While some BD patients may experience rapid cycling of episodes within hours or days, in others, episodes are separated by months or years (Carvalho et al., 2014). BD patients may also have common comorbidities such as anxiety (Spoorthy et al., 2019), substance abuse (Jawad et al., 2018), and psychotic features (Maggioni et al., 2017). In addition, BD patients are at a higher risk of performing suicidal behaviour compared to other psychiatric patients (Jamison, 2001).

Both genetic and environmental factors are recognised to be important in the development of BD phenotypes. Environmental risk factors such as adverse childhood experiences (ACE) and childhood maltreatment (CM) have been closely associated with BD phenotype development. ACEs describe adverse events, such as the death or divorce of a caregiver, serious illness, or hospitalisation. According to the past meta-analysis by Palmier-Claus et al. (2016), BD patients were 2.63 times more likely to have experienced ACE. ACE has also been found to play a significant role in the risk of relapse in BD patients (Hosang et al., 2010). Meanwhile, CM describes traumatic abusive events. CM is separated into emotional abuse (EA), physical abuse (PA), and sexual abuse (SA), as well as emotional neglect (EN) and physical neglect (PN;

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Gilbert et al., 2009). CM is commonly recognised as a more severe form of ACE. CM has also been associated with more severe and complex BD phenotypes (Agnew-Blais and Danese, 2016). These include earlier age of onset and a higher risk of comorbidities such as anxiety disorder, substance misuse disorder, suicide attempts, and increased mood episodes.

Examining the influence of both genes and the environment is essential for understanding BD symptom outcomes (Quidé et al., 2020). It is commonly believed that existing biological vulnerabilities interact with the later experiences such ACE and lead to more complex mental health conditions. Thus, individuals who already carry a high genetic risk for BD are at even higher risk of developing BD if they have experienced ACE (Duffy et al., 2020). Recently, researchers have begun exploring such gene and environment interaction effects in predicting the development of BD sub-phenotypes (Anand et al., 2015; Aas et al., 2020; Park et al., 2020). These studies were based on the development of genome-wide association studies (GWAS) and polygenic risk score (PRS) calculations. The calculation of polygenic risk scores generally has two primary purposes (1) to predict the likelihood of developing the outcome of interest by synthesizing existing GWAS information into a single measure; (2) to estimate the predictive ability of known effects. Therefore, PRSs can classify the relative risk of a specific outcome for an individual within a population and have been applied in different gene-environment interaction studies.

However, there have been recent conflicts regarding how BD PRS is associated with the number of ACEs and how BD PRS interacts with ACE in the predictions of various BD sub-phenotypes (Park et al., 2020; Aas et al., 2020). For example, Aas et al. (2020) showed that BD PRS might only interact with childhood maltreatment in predicting the risk of rapid cycling. In comparison, Park et al. (2020) observed another interaction effect in predicting the age at onset (AAO) of BD. These differences between results may be due to different ACE definitions or clinical heterogeneity between sample cohorts. For instance, Aas et al.'s (2020) measures of ACE were mainly CM, while Park et al.'s (2020) measures were mainly ACE, with an additional CM item on physical abuse. Thus, there was no clear separation on the ACE concept. Another major limitation of both these past studies is that they did not consider an individual's genetic liability to other psychiatric disorders (Grigoroiu-Serbanescu et al., 2020). Given that BD has a high level of overlapping clinical heterogeneity and shared genetic risk with other psychiatric disorders, it seems necessary to include multiple psychiatric PRSs and their interactions with ACE to predict phenotype development (Coombes et al., 2020; Baldwin et al., 2022).

Differentiating between attention-deficit/hyperactivity disorder (ADHD) and BD remains as a challenge for clinicians, as these two disorders have extensive symptom overlap, reciprocal comorbidity, and overlapping age of onset periods (Brus et al., 2014; Marangoni et al., 2015). ADHD and BD were proven to be genetically correlated (r_g 0.121) and share common risk variants (O'Connell et al., 2021). Children with ADHD were more likely to have higher ACE exposure than children without ADHD (Brown et al., 2017). And the higher exposure to ACE may also increase their risks to develop ADHD (Crouch et al., 2021). The presence of ADHD symptoms can be an indication of worse depression presentation (Powell et al., 2021) and is linked to rapid cycling between BD episodes (Aedo et al., 2018).

In addition, genetic predisposition to Major Depressive Disorder (MDD) can be predictive of specific patterns of depression symptoms (Martínez-Levy et al., 2021). An additive interaction effect between genetic predisposition to depression and trauma exposure has been observed on depressive symptoms among MDD patients (Thorp et al., 2023). Meanwhile, schizophrenia (SCZ) PRS can also be predictive of schizophrenia patients' psychotic symptoms, cognition, illness severity, and diagnostic changes (Jonas et al., 2019). However, no previous study specifically examined how these different psychiatric genetic liabilities interact with environment risk factors such as ACE in predicting the development of BD sub-phenotypes.

To address these research gaps, we wanted to replicate past gene x environment (GxE) findings on ACE and BD PRS. We also wanted to explore these multiple PRSs' prediction effects of BD sub-phenotype development. Thus, our research had three main aims:

(1) to clarify the association between BD PRS and ACE;
(2) to investigate how the number of ACEs interacts with multi-PRSs in the predictions of distinct BD sub-phenotypes;
(3) to understand whether ACE could predict BD sub-phenotype development and change the interaction effect when CM items are absent.

Our objective was to use multiple linear and logistic regressions to explore the association between the PRSs and the ACE numbers, including their interaction effect in predicting the associated sub-phenotypes. We hypothesized that the multi-PRSs would interact with ACEs in predicting the sub-phenotype development. People with higher PRSs (BD/ADHD/MDD/SCZ) and more ACEs were predicted to have developed BD at a younger age and developed more severe or complex sub-phenotypes, such as psychosis symptoms, suicide ideation, and rapid cycling.

2. Methods

2.1. Participants

All BD cases received an ICD10 diagnosis of BD from a UK National Health Service (NHS) psychiatrist (World Health Organization, 1992). Ancestrally matched healthy controls (n = 1818) were recruited from the National Health Service (NHS) blood transfusion service and from study sites where case participants were also being recruited. The controls were screened for an absence of a lifetime history of the following disorders: schizophrenia and any other psychosis, major affective or schizoaffective disorders, eating disorders, alcohol/drug addiction, and obsessive-compulsive disorders. All participants were of English, Scottish, Welsh, or Irish descent and had at least three out of four grandparents of the same descent. The study was approved by the NHS Metropolitan Multi-centre Research Ethics Committee (MREC/03/11/090). All participants read an approved information sheet and signed a physical informed consent form.

2.2. Study measures

Semi-structured interviews were performed with BD participants using the lifetime version of the Schizophrenia and Affective Disorder Schedule (SADS-L; Spitzer et al., 1978), the 90-item Operational Criteria Checklist (OPCRIT; McGuffin et al., 1991) and the Children Life Event Questionnaire (CLEQ; Monaghan et al., 1979). In a subset of participants, the 25-item version of the Wender Utah Rating Scale (WURS) was used to measure childhood ADHD symptoms (Ward, 1993; Grigoroiu-Serbanescu et al., 2020). A subset of the participants received lithium treatment prior to the assessment and their response to lithium was scored using data from clinicians and the research participant. Where these scores differed the clinician's rating was used. The data was coded in a binary format to differentiate between responders and non-responders. BD age of onset, presence of psychosis symptoms, presence of suicide ideation, and presence of rapid cycling were selected for analyses in the current study. These variables were chosen because of their relevance to BD according to past reviews (Palmier-Claus et al., 2016; Escamilla and Zavala, 2008). We also sought to replicate previous findings from Park et al., and Aas et al., (Park et al., 2020; Aas et al., 2020).

In this research, BD age of onset was defined as the earliest age at which symptoms began to cause subjective distress or impair functioning or at which medical advice was sought for psychiatric reasons. Age at onset was stored as a continuous variable (OPCRIT item 4). The

presence of psychotic symptoms was defined as whether the participants disclosed any symptoms of impaired reality testing (any presence of OPCRIT items 54–77; see Supplementary Material). The presence of suicide ideation was defined as whether the participants with BD reported thoughts of death (not necessarily their own), thinking of suicide, wishing to be dead, or attempting to kill themselves (OPCRIT item 43). The presence of rapid cycling was defined as whether the patient ever had four or more mood disturbances in one year. These latter three variables were stored in binary format.

ACEs were measured separately using the CLEQ, an adaption of the children's life events inventory, which records the ACE experienced before the age of 16 (Monaghan et al., 1979). The CLEQ included 13 binary "YES" or "No" questions. The first 12 questions had content such as the death of a parent; the death of a brother or sister; serious illness; hospitalisation of a parent; teenage pregnancy; suspension from school (see CLEQ in Supplementary Material). The last question required the participants to specify other significant adverse life events experienced as a child if they answered "YES." Due to the variability of events recorded with question 13, we only focused on the first 12 CLEQ questions. If the participant answered "Yes" to any of the first 12 questions, this indicated the experience of ACE. The number of "YES" answers to all 12 questions indicated how many ACEs each participant had been through.

2.3. Genotyping, imputation, and quality control

Genome-wide single nucleotide polymorphism data was available for the BD and healthy control subjects. The data was generated in two waves at the Broad Institute, Boston, MA, US, using the Illumina PsychArray and Illumina Global Screening Array (GSA). The quality control and imputation methods used for the PsychArray had been described elsewhere (Grigoroiu-Serbanescu et al., 2020). The genotype data from the GSA underwent equivalent quality control and imputation procedures as for the PsychArray.

2.4. Calculation of the polygenic risk score (PRS)

Patients' multi-PRSs (BD/ADHD/MDD/SCZ) were computed using imputed data from the PsychArray and GSA with the PRS-CS-auto method which provides a single score for each sample without any thresholds (Ge et al., 2019). The PRS-CS-auto method was chosen over other methods since it outperformed other existing methods according to the simulation studies by Ge et al. (2019). Pain et al. (2021) also found PRS-CS-auto to be the best of the pseudo-validation PRS methods. PRS-CS is distinct as it utilises a high-dimensional Bayesian regression framework and places a continuous shrinkage (CS) before SNP effect size calculations. Such procedures result in substantial computational advantages and enable multivariate modelling of local LD patterns, which makes PRS-CS robust to varying genetic architectures.

The application of the PRS-CS method required an LD reference panel and reference GWAS summary statistic, which help infer the posterior effect sizes of SNPs. We chose the European sample from The 1000 Genomes Project Consortium (2010) as our LD reference panel. The BD reference GWAS came from Mullins et al. (2021) which included the PsychArray samples used in the current study. We therefore used summary statistics generated without the overlapping samples to avoid confounding. Our ADHD reference GWAS came from the Psychiatric Genomics Consortium, a meta-analysis including 38,691 ADHD cases (Demontis et al., 2023). We used data from Howard et al.'s (2019) for MDD GWAS which excluded UK Biobank and 23andMe data covering 170,756 cases and 329,443 controls. The SCZ GWAS came from Trubetskoy et al. (2022) which covered 68,676 cases and 96,079 controls. We adapted all GWAS samples to be based on subjects of European ancestry and data from the samples that we had contributed to the PGC schizophrenia analyses excluded our own lab's data. The new GWAS generation followed the same procedures as described by each GWAS paper. The reference GWAS sample sizes were calculated using the effective sample size method (Neff) as $4/(1/N\_cases + 1/N\_controls)$, where N_cases is the number of cases and N_controls is the number of controls. Thus, the reference GWAS sample sizes were 103,136 for BD, 45,685 for ADHD, 449,856 for MDD and 160,197 for SCZ.

We used the mean and standard deviation of the PRS from the healthy controls to standardise the PRS data of the BD cases. This was performed separately for the PsychArray and the GSA data. By standardising the PRSs to a normal distribution with mean = 0 and SD = 1, the PRSs from the PsychArray and GSA could be combined directly and applied easily into regression models as continuous variables. Also, the standardisation of the PRS allowed the conversion of an individual's PRS to quantiles for risk comparison across individuals.

2.5. Statistical analysis

CLEQ and PRS data was available for 885 BD subjects, 640 from the PsychArray and 245 from the GSA. The participants were first divided into two groups based on the presence of ACE and then compared for the difference in characteristics. Wilcoxon rank sum tests, chi-squared tests and independent *t*-tests were applied according to the variable type and distribution. To illustrate the association between ACEs and multi-PRSs, we first conducted pairwise comparisons using simple t-tests taking ACE as a categorical variable. Then we conducted linear regressions using ACE total number and multi-PRSs taking appropriate adjustments.

Next, we performed multiple linear and logistic regression analyses to assess how ACE, multi-PRSs and their interactions predict the development of selected BD sub-phenotypes. The assumptions for linear and logistic regressions were pre-checked and found to be satisfactory for each regression. Then the CLEQ total score, one PRS, or their interaction term, was each added into the model by sequence. Finally, we divided the samples into four quantile groups based on their BD/ADHD PRS values respectively. We conducted additional logistic regressions taking the lowest PRS group as reference to test if people with higher BD/ADHD PRSs would have higher odds of experiencing ACE or developing the selected sub-phenotypes. The presence of ACE was added as a moderator. We carried out additional interaction analyses to examine if there were significant differences between each PRS quantile group and the presence of ACE, and the interactions between ADHD and BD PRS were also examined (See Supplementary Results).

The participants' BD age of onset and sex were included as covariates in all analyses except for age of onset where only sex was included. The genotyping chip type and the first three principal components from GWAS population stratification were included in addition for all regression analyses involving PRS to account for chip and ancestry confounding. To further account for genotyping difference, we conducted additional sensitivity analyses using PRSs generated from only overlapping risk variants from both chips (See Supplementary Results). All these described analyses were done using RStudio with R version 4.1.3 (R Core Team, 2021).

To account for multiple testing, we applied False Discovery Rate (FDR) correction method (Benjamini and Hochberg, 1995) to the results obtained using the p.adjust function in R for each set of analyses. The FDR method was chosen over the others as it gives a good illustration of results and has been applied in previous studies involving PRS (Grigoroiu-Serbanescu et al., 2020).

3. Results

3.1. Sample descriptions

Overall, the participants had a median age of 49 (ranging from 19 to 95) when they received the assessment. 62 % of the participants had experienced at least one ACE before the age of 16 (see Table 1). The samples contained a high proportion of females (60 %) and type 1 BD patients (65 %). The two groups did not differ in sex or BD type ratios.

Table 1
Participants' Demographics and Clinical Characteristics concerning ACE Presence.

Variables	N	Overall $N = 885$	Group without ACE $N = 338$	Group with ACE $N = 547$	*p*-Values
Age at interview	728	49 (39, 59)	50 (42, 60)	48 (38, 57)	**0.003**[a]
Sex (Females)	885	532 (60 %)	199 (59 %)	333 (61 %)	0.600[b]
BD type	885				0.400[b]
BD type 1		572 (65 %)	224 (66 %)	348 (64 %)	
BD type 2		141 (16 %)	56 (17 %)	85 (16 %)	
Schizoaffective BD		172 (19 %)	58 (17 %)	114 (20 %)	
Childhood ADHD	191	37.07 (22.58)	39.00 (21.03)	35.83 (23.54)	0.333[c]
Lithium responders	418	152 (36 %)	65 (38 %)	87 (35 %)	0.612[b]
Age of BD onset	746	19 (16, 29)	22 (17, 29)	18 (15, 28)	**0.009**[a]
Psychotic symptoms	844	598 (71 %)	222 (69 %)	376 (72 %)	0.400[b]
Suicide ideation	814	613 (75 %)	217 (71 %)	396 (78 %)	**0.017**[b]
Rapid cycling	499	215 (43 %)	61 (36 %)	154 (47 %)	**0.016**[b]
BD PRS	885	0.71 (1.05)	0.72 (1.01)	0.70 (1.08)	0.819[c]
ADHD PRS	885	0.02 (1.03)	−0.10 (1.05)	0.10 (1.01)	**0.005**[c]
MDD PRS	885	0.26 (1.00)	0.19 (0.99)	0.30 (1.00)	0.113[c]
SCZ PRS	885	0.52 (0.97)	0.59 (0.96)	0.48 (0.97)	0.101[c]

Notes. ACE, adverse childhood experience; childhood ADHD (scores from the Wender Utah rating scale); BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; SCZ, schizophrenia disorder; IQR, interquartile range; SD, standard deviation; PRS, polygenic risk score.
In bold *p* values are below 0.05 threshold.
[a] Wilcoxon rank sum test; median (IQR).
[b] Pearson's Chi-squared test of independence; n (%).
[c] Independent *t*-test; mean (SD).

The participants also did not differ in childhood ADHD (defined using the WURS) and responses to lithium. The participants had a median BD onset age of 19. The participants' age at interview and BD onset age was earlier in subjects who had experienced at least one ACE (see Table 1). The participants also differed in the presence of suicide ideation ($p = 0.017$) and rapid cycling ($p = 0.016$). We found strong evidence to suggest that the presence of ACE was associated with an increase in ADHD PRS ($p = 0.005$).

3.2. Correlations between multi-PRSs (BD/ADHD/MDD/SCZ) and the CLEQ scores

We found no evidence supporting any associations between BD PRS and ACE scores using pairwise comparisons (see Fig. 1) or linear regressions with (coefficient = −0.037; 95 % CI: −0.146 to 0.073, $p = 0.511$) or without any adjustments (coefficient = −0.051; 95 % CI: −0.149 to 0.046, $p = 0.300$). However, we found strong evidence suggesting that the participants with none and three or more ACE differed in ADHD PRS (see Fig. 1). The unadjusted linear regression results also indicated that higher ADHD PRS increased the susceptibility to ACE reporting (coefficient = 0.198, 95 % CI: 0.099 to 0.296, $p < 0.001$). The association was even stronger after adding in adjustments (coefficient = 0.231, 95 % CI: 0.118 to 0.345, $p < 0.001$). Weak evidence was found to suggest the association between MDD PRS and ACE scores (coefficient = 0.103, 95 % CI: <0.001 to 0.205, $p = 0.049$) the evidence remained after adding in adjustments (coefficient = 0.127; 95 % CI: 0.012 to 0.243, $p = 0.031$). No evidence could be found for SCZ PRS before (coefficient = −0.099, 95 % CI: −0.204 to 0.006, $p = 0.066$) or after adjustment (coefficient = −0.043, 95 % CI: −0.161 to 0.074, $p = 0.470$). And no other pair-wise comparison results survived correction for multiple testing (see Fig. 1).

3.3. ACE/BD PRS associations & interaction with phenotypes

We found substantial evidence to suggest that each unit increase in BD PRS would increase the odds of having psychotic symptoms by exp.(0.258) = 1.294 (95 % CI 1.093 to 1.538; *FDR_p* = 0.035; See Table 2). We also found strong evidence that each unit increase in ACE number would increase the odds of having rapid cycling by exp.(0.228) = 1.256 (95 % CI 1.084 to 1.463; *FDR_p* = 0.035). We found some tendency that ACE might be associated with an earlier age of onset. We carried out additional subgroup analyses to clarify the effect. We found strong evidence to suggest that only males who experienced ACE would have earlier age of onset (coefficient − 1.568, 95 % CI: −2.568 to −0.567, $p = 0.002$).

Overall, we did not observe any interaction effect between ACE number and BD PRS in predicting any of the sub-phenotypes examined. (See Table 2).

3.4. ADHD PRS associations & interaction with phenotypes

We found strong evidence to suggest that each unit increase in ADHD PRS led to an increase in the odds of developing rapid cycling BD by exp.(0.369) = 1.45 (95 % CI 1.20–1.75; *FDR_p* = 0.002). No other symptoms were associated with the ADHD PRS and no significant interaction effect between ACE number and ADHD PRS in predicting these sub-phenotypes was observed (see Table 2).

3.5. MDD/SCZ PRS associations & interaction with phenotypes

We could not find any evidence to suggest MDD and SCZ PRS would predict any of these selected sub-phenotypes (see Table 3). And we observed no interaction effect.

3.6. PRS quantile analyses

Given that no effect could be observed from MDD/SCZ PRS, participants were only divided into quantile groups based on their BD/ADHD PRSs for ACE influence (see odds results in Supplementary Table 3). Overall, we found strong evidence to suggest that BD patients in the highest ADHD PRS quantile group had 2.009 higher odds of having experienced ACE than those in the lowest ADHD PRS quantile group (95 % CI 1.230 to 3.313, $p = 0.006$ *FDR_p* = 0.046; Fig. 2A).

BD patients in the highest BD PRS quantile group had 1.917 higher odds of developing psychotic symptoms than those in the lowest BD PRS quantile group (95 % CI 1.166 to 3.182, $p = 0.011$, *FDR_p* = 0.234; Fig. 2B). But, we did not observe any evidence for association between either PRS and the presence of suicide ideation (Fig. 2C). Meanwhile, BD patients in the highest ADHD PRS quantile group had 2.642 higher odds of developing rapid cycling than those in the lowest ADHD PRS quantile group (95 % CI 1.393 to 5.097, $p = 0.003$, *FDR_p* = 0.026; Fig. 2D). We performed additional interaction analyses to further examine group differences (see Supplementary Table 4). We only found tendency for an interaction effect between the two PRSs in the predictions of ACE presence (see details in Supplementary Results).

4. Discussion

This study used multi-PRSs to dissect their association and interaction with ACE for predicting BD sub-phenotypes. Our study

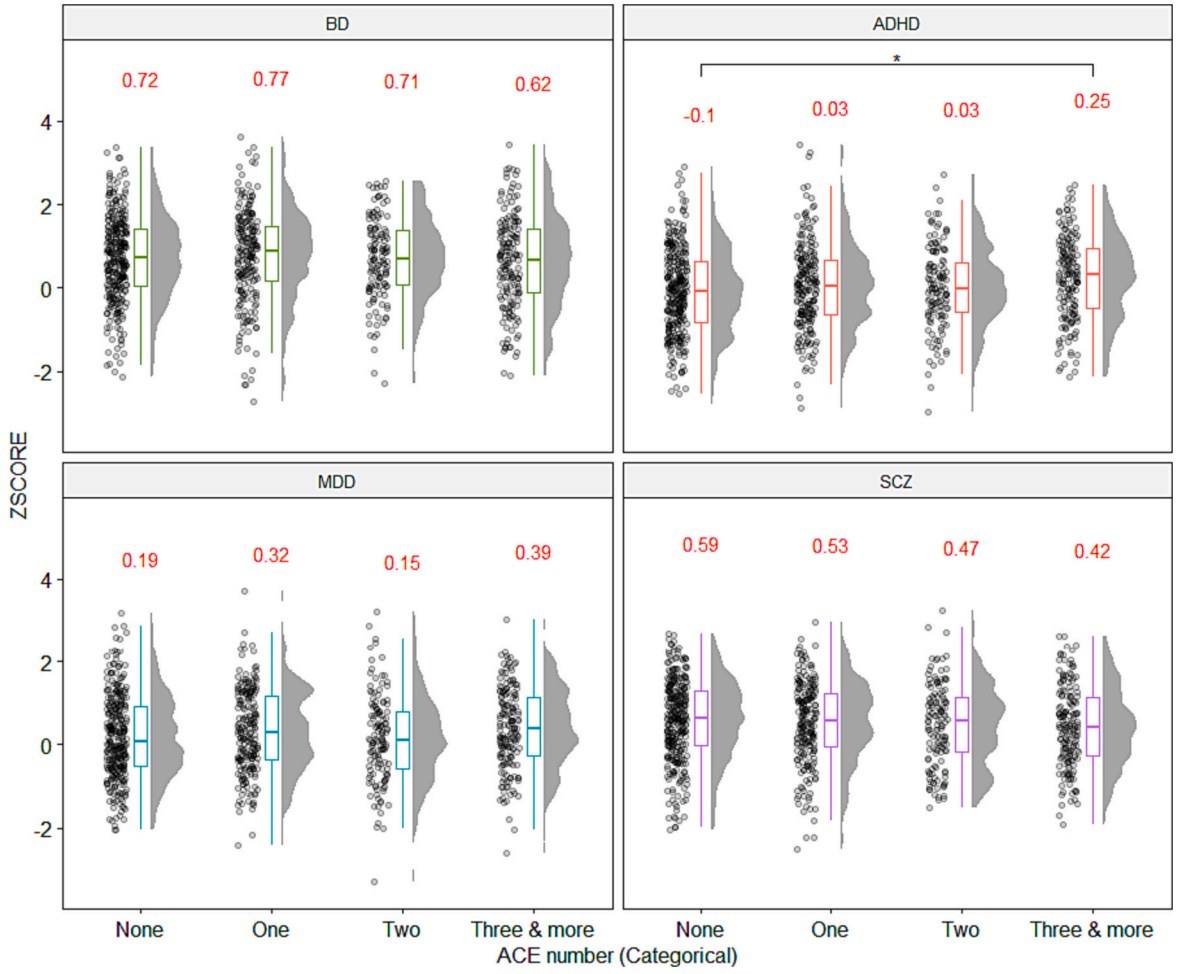

Fig. 1. Mean polygenic risk scores for ADHD, BD, MDD, and SCZ across ACE groups.
Notes. ACE, adverse childhood experience; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; SCZ, schizophrenia disorder.
The above numbers corresponded to PRS means for each ACE group.
* in the current plot, p values survived FDR multiple testing correction for simple *t*-tests for pair-wise comparison.

demonstrated that BD participants with higher ADHD PRS tended to report more ACEs, whereas BD PRS was not associated with ACEs reporting. We also found some weak evidence to suggest that BD patients with higher MDD may experience more ACE. In addition, our results suggested that the BD patients with higher BD PRS would have increased odds of developing psychotic symptoms. Although both increased ACE number and ADHD PRS were associated with increased odds of developing rapid cycling among BD patients, no additive interaction effect could be observed.

Past studies had conflicts regarding whether the increase in ACE numbers is associated with BD PRS positively (Park et al., 2020) or negatively (Aas et al., 2020). Our results still could not provide a specific answer since we could not identify any significant results between BD PRS and the reported number of ACE across multiple analyses. However, our results suggested that increased ADHD PRS was associated with more ACE reporting. These results are consistent with National Survey of Children's Health studies which observed that children with ADHD symptoms may more likely experience ACE (Brown et al., 2017; Crouch et al., 2021). We also found weak evidence for the positive association between MDD PRS and ACE. Thus, it seems more likely that BD patients' genetic liability to other psychiatric disorders together accounted for the presence of ACE. However, it should not be assumed that the exposure to ACE is determined by genetic risk, given that most recorded ACE were passive. In this case, a possible explanation could be that these participants' parents not only transmitted genetic risk variants linked to psychiatric disorders to their child but also provided adverse environments (Baldwin et al., 2022).

Most previous research has shown that an increasing number of ACEs is associated with a lower age of BD onset (Anand et al., 2015; Aas et al., 2020; Park et al., 2020). Our study also identified the same pattern in results for ACE presence. Only the study by Park et al. (2020) found an additive interaction effect between BD PRS and ACE for predicting earlier BD age of onset. Our results and the other research did not identify such an interaction pattern (Aas et al., 2020). It should be noted that the study by Park et al. (2020) was purely based on BD type 1 patients. Our samples contained 65 % BD type 1 patients, and the study by Aas et al. (2020) contained 74 % BD type 1 patients. Thus, differences between study samples in the genetic liability to other psychiatric disorders may have influenced these results (Guzman-Parra et al., 2021). In addition, although another study by Anand et al. (2015) included 1995 BD type 1 patients, they still could not identify significant interaction between any single SNP and the presence of childhood traumatic events on the prediction of BD age at onset. However, they found that only SNPs in or near genes coding for calcium channel activity-related proteins (Gene Ontology: 0005262) were more likely to show an interaction effect. Thus, if the gene x environment interaction exists in predicting BD age of onset, it might be small and require large sample sizes to detect. Given that the study by Park et al. (2020) contained 1615 BD cases,

Table 2
Results of Multiple Regression Analyses with Adjustments based on ACE (total score) and BD/ADHD PRS.

Variables	Estimated coefficient	Standard error	Confidence intervals (95 %)	Reference values	*p*	*FDR_p*
Age at onset[a]						
ACE	−0.835	0.330	−1.482, −0.188	−2.543	**0.012**	0.104
BD PRS	−0.315	0.466	−1.230, 0.600	−0.677	0.499	0.877
BD Interaction	−0.316	0.328	−0.960, 0.328	−0.963	0.336	0.765
ADHD PRS	−0.624	0.491	−1.588, 0.339	−1.273	0.204	0.717
ADHD Interaction	−0.421	0.341	−1.090, 0.248	−1.236	0.217	0.717
Presence of psychotic symptoms[b]						
ACE	0.069	0.063	−0.052, 0.195	1.091	0.275	0.761
BD PRS	0.258	0.087	0.089, 0.430	2.974	**0.003**	**0.035**
BD Interaction	−0.074	0.063	−0.197, 0.051	−1.177	0.239	0.718
ADHD PRS	−0.043	0.090	−0.221, 0.134	−0.478	0.633	0.878
ADHD Interaction	0.005	0.065	−0.122, 0.133	0.074	0.941	0.991
Presence of suicide ideation[b]						
ACE	0.178	0.074	0.037, 0.328	2.398	**0.016**	0.119
BD PRS	−0.048	0.093	−0.231, 0.134	−0.514	0.607	0.878
BD Interaction	−0.088	0.072	−0.229, 0.053	−1.229	0.219	0.717
ADHD PRS	0.055	0.098	−0.137, 0.248	0.562	0.574	0.878
ADHD Interaction	−0.007	0.077	−0.156, 0.146	−0.095	0.924	0.991
Presence of rapid cycling[b]						
ACE	0.228	0.076	0.081, 0.381	2.992	**0.003**	**0.035**
BD PRS	−0.106	0.103	−0.310, 0.095	−1.032	0.302	0.765
BD Interaction	−0.041	0.085	−0.209, 0.125	−0.479	0.632	0.878
ADHD PRS	0.495	0.121	0.262, 0.738	4.080	**<0.001**	**0.002**
ADHD Interaction	0.144	0.090	−0.30, 0.324	1.600	0.109	0.563

Notes. ACE, adverse childhood experience; PRS, polygenic risk score; BD, bipolar disorder; ADHD, attention deficit hyperactivity disorder.
FDR_p = false discovery rate corrected *p* values for multiple testing.
In bold *p* values were significant before correction or survived FDR correction for multiple testing.
All results were adjusted for participants' BD age of onset and sex (except for age of onset where only sex was included).
PRS & interaction results were adjusted for chip type and the first three principal components from GWAS population stratification in addition to sex and age of onset.
[a] Multiple linear regression analyses, reference value t.
[b] Multiple logistic regression analyses, reference value z.

Table 3
Results of Multiple Regression Analyses with Adjustments based on Total ACE Number and MDD/SCZ PRS.

Variables	Estimated coefficient	Standard error	Confidence intervals (95 %)	Reference values	*p*	*FDR_p*
Age at onset[a]						
MDD PRS	−0.472	0.494	−1.442, 0.498	−0.956	0.340	0.765
MDD Interaction	−0.070	0.331	−0.719, 0.579	−0.212	0.832	0.991
SCZ PRS	0.021	0.501	−0.961, 1.004	0.043	0.966	0.991
SCZ Interaction	−0.299	0.358	−1.001, 0.403	−0.837	0.403	0.853
Presence of psychotic symptoms[b]						
MDD PRS	−0.052	0.091	−0.232, 0.127	−0.574	0.566	0.878
MDD Interaction	−0.001	0.064	−0.128, 0.123	−0.017	0.987	0.991
SCZ PRS	0.118	0.092	−0.063, 0.299	1.280	0.201	0.717
SCZ Interaction	−0.134	0.069	−0.251, 0.021	−1.643	0.100	0.563
Presence of suicide ideation[b]						
MDD PRS	−0.041	0.098	−0.233, 0.151	−0.418	0.676	0.888
MDD Interaction	−0.002	0.074	−0.149, 0.143	−0.028	0.978	0.991
SCZ PRS	−0.001	0.100	−0.199, 0.195	−0.011	0.991	0.991
SCZ Interaction	0.021	0.086	−0.148, 0.190	0.241	0.810	0.991
Presence of rapid cycling[b]						
MDD PRS	0.086	0.111	−0.131, 0.304	0.776	0.438	0.876
MDD Interaction	0.032	0.081	−0.128, 0.193	0.397	0.691	0.888
SCZ PRS	0.052	0.109	−0.161, 0.267	0.477	0.634	0.878
SCZ Interaction	0.052	0.080	−0.105, 0.212	0.641	0.521	0.878

Notes. ACE, adverse childhood experience; MDD, major depressive disorder; SCZ, schizophrenia disorder.
FDR_p = false discovery rate corrected p values for multiple testing.
All results were adjusted for participants' BD age of onset and sex (except for age of onset where only sex was adjusted).
PRS & interaction results were adjusted for chip type and the first three principal components from GWAS population stratification in addition to sex and age of onset.
[a] Multiple linear regression analysis, reference value t.
[b] Multiple logistic regression analysis, reference value z.

much larger than our sample size of 885 and Aas et al.'s (2020) sample size of 402. The sample sizes might explain the difference in the results. Another possible explanation for the difference on age of onset could be sex differences. Our additional sub-group analyses found that only males who experienced ACE would have earlier age of onset.

Our results on psychosis symptoms were consistent with Aas et al. (2020), which similarly recorded the psychosis variable in terms of the episode. Our results showed that people with a higher BD PRS may be more likely to show psychotic symptoms. One recent study also found that BD PRS might relate to the manic symptoms in participants with a history of psychotic episodes (Ahangari et al., 2022). However, we could not identify any significant association between ACE and psychosis symptoms or evidence for an interaction effect. Upthegrove et al. (2015) argued that the different ACE types might influence the development of

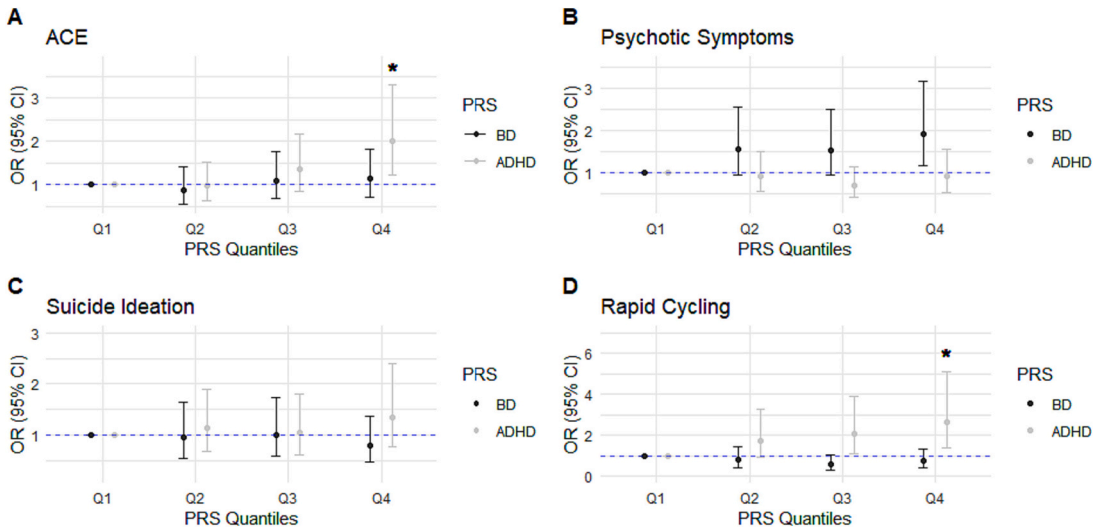

Fig. 2. The odds ratios of having ACE and developing the three selected sub-phenotypes with reference to PRS quantile levels.
Notes. OR odds ratio, CI confidence intervals, PRS polygenic risk scores.
Q1, 0–25 %; Q2, 25 %–50 %; Q3, 50 %–75 %; Q4 75%–100 %
The participants' sex, age of onset, the genotyping chip type and the first three principal components from GWAS population stratification were included as covariates in all analyses.
The presence of ACE was included as a moderator in the PRS models for the three sub-phenotypes.
* in the current plot, *p* values survived FDR multiple testing correction.

psychosis symptoms differently. Childhood abuse had the strongest associations. Although Aas et al.'s (2020) study focused on CM, covering all abuse items, the associations and interaction effects were still insignificant. Thus, it seemed likely that these psychotic symptoms in BD subjects might be more genetically predetermined.

We found that the ADHD PRS in BD subjects may be highly associated with the presence rapid cycling. However, we should be careful when interpreting the findings on rapid cycling. In contrast to Aas et al. (2020), we could not find an interaction between BD PRS and ACE or between ADHD PRS and ACE on rapid cycling. Our results showed that the increase in ACE number and ADHD PRS might independently increase the odds of rapid cycling. And they also positively associated with each other. Such results may indicate the presence of mediation effects which requires further examination.

In addition, we could not find any prediction effects from MDD or SCZ PRS. The previous studies which found these two PRSs' prediction effects were based on samples which were of the same category MDD and SCZ patients (Thorp et al., 2023; Jonas et al., 2019). Although these two disorders were also genetically correlated with BD, the current results suggest that they are underpowered to predict the development of any BD sub-phenotype symptoms.

Overall, we could not identify any significant interaction effect in any models. We anticipated that cases with more ACE and higher PRSs would develop more severe phenotypes. However, our results suggested that different levels of PRS might not significantly influence the relationship between ACE and other BD phenotypes. Meanwhile, the association between the PRS and sub-phenotypes did not significantly differ according to the number of ACE participants experienced. Such conflicts might be because past studies that found the interaction effects included more severe forms of ACE, such as CM, covering abuse and trauma (Aas et al., 2020; Park et al., 2020). However, the ACE measurement in our study only included ACE without any traumatic events such as abuse and neglect. Thus, the interaction effects may have been attenuated in our study. However, our results also showed evidence that even ACE without any CM items could be significant predictors for predicting different sub-phenotypes. Overall, such results highlight the importance of considering different ACE definitions for future interaction studies.

4.1. Strengths

Our study first used the more advanced PRS-CS-auto method and the latest reference GWAS to calculate multi-PRSs. Thus, a straightforward explanation for the difference between our results and those from past studies might be that the multi-PRSs used here were more powerful predictors of a subject's genetic liability to psychiatric disorders. We also used robust correction method for selecting results from the statistical analyses. Concerning the link between multi-PRSs and ACEs, we replicated past studies' analyses and ran additional tests. By focusing on ACE items without any CM items, our results consolidated ACE's potential in predicting different phenotype developments. Such results also highlighted that future studies should consider the ACE definition when conducting gene-environment interaction studies. In addition, our findings confirmed the importance of considering multiple psychiatric PRSs in BD subjects and their interactions with ACE for improving phenotype predictions. Future larger-scale studies with more precise separation of ACE types, more psychiatric PRSs and more of their interactions are encouraged.

4.2. Limitations

This study's findings could be limited by its case-control recruitment and cross-sectional data collection methods. Retrospective data such as analysed in this study is always subject to potential recall bias. The participants had a median age of 49 at the interview assessment, but the CLEQ required them to recall life events before age 16. All data was collected directly from the participants. If the BD patients developed delusions or hallucinations regarding their childhood experiences, it would be impossible for us to tell. Also, our study did not separate ACE severity or phenotype severity. We focused on only the ACE without any CM items. Thus, we could only make inferences but not compare ACE and CM items' different effectiveness. In addition, our findings were limited by our sample size and sample characteristics (mixed BD types). Future studies can use mixed models that deal better with missing data, characteristic differences, unequal sample sizes, and non-independence of samples. Given that all samples are Europeans, our findings might also have limited transferability. Finally, neither the PRS nor ACEs could

explain a large amount of individual variation. Even though we found some links between PRS and phenotypes that might be important in the clinic, these results were still a long way from letting us predict how an individual's phenotype will develop.

5. Conclusion

BD is a complex and heterogeneous disorder. Both genetic and environmental risk factors influence its phenotypic development. In this context, future larger-scale studies with more precise separation of ACE types, more psychiatric PRSs, and more of their interactions can better illustrate the phenotype development predictions among BD patients. Together, these efforts will support better BD prognosis, risk prediction, treatment allocation, and harm prevention.

CRediT authorship contribution statement

All authors participated in the design of this study. Author KY led the writing of the manuscript. Authors TV and AM supported the statistical analyses. All authors contributed to revise drafts and approved the final manuscript.

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Ethical approval and data availability statement

The data collection procedures were approved by the NHS Metropolitan Multi-centre Research Ethics Committee (MREC/03/11/090). The data is available by request.

Declaration of competing interest

The authors declared no potential conflict with respect to the research, authorship, and/or publication of this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.08.116.

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