Psychological Medicine

cambridge.org/psm

Original Article

Cite this article: Baek JH, Lee D, Lee D, Jeong H, Cho E-Y, Ha TH, Ha K, Hong KS (2024). Exploring intra-diagnosis heterogeneity and inter-diagnosis commonality in genetic architectures of bipolar disorders: association of polygenic risks of major psychiatric illnesses and lifetime phenotype dimensions. *Psychological Medicine* 1–7. https://doi.org/10.1017/S003329172400120X

Received: 4 October 2023
Revised: 26 March 2024
Accepted: 26 April 2024

Keywords:
bipolar disorder; cross-disorder commonality; deep phenotyping; polygenic risk score

Corresponding author:
Kyung Sue Hong;
Email: kyungsue.hong@ubc.ca

Exploring intra-diagnosis heterogeneity and inter-diagnosis commonality in genetic architectures of bipolar disorders: association of polygenic risks of major psychiatric illnesses and lifetime phenotype dimensions

Ji Hyun Baek[1,2], Dongbin Lee[3], Dongeun Lee[1], Hyewon Jeong[4], Eun-Young Cho[4], Tae Hyon Ha[5], Kyooseob Ha[6,7] and Kyung Sue Hong[6,7]

[1]Department of Psychiatry, Sunkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea; [2]Dauten Family Center for Bipolar Treatment Innovation, Massachusetts General Hospital, Boston, USA; [3]Department of Digital Health, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Samsung Medical Center, Seoul, Korea; [4]Samsung Biomedical Research Institute, Seoul, Republic of Korea; [5]Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [6]Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada and [7]Department of Psychiatry, Lions Gate Hospital – Vancouver Coastal Health Authority, British Columbia, Canada

Abstract

Background. Bipolar disorder (BD) shows heterogeneous illness presentation both cross-sectionally and longitudinally. This phenotypic heterogeneity might reflect underlying genetic heterogeneity. At the same time, overlapping characteristics between BD and other psychiatric illnesses are observed at clinical and biomarker levels, which implies a shared biological mechanism between them. Incorporating these two issues in a single study design, this study investigated whether phenotypically heterogeneous subtypes of BD have a distinct polygenic basis shared with other psychiatric illnesses.

Methods. Six lifetime phenotype dimensions of BD identified in our previous study were used as target phenotypes. Associations between these phenotype dimensions and polygenic risk scores (PRSs) of major psychiatric illnesses from East Asian (EA) and other available populations were analyzed.

Results. Each phenotype dimension showed a different association pattern with PRSs of mental illnesses. PRS for EA schizophrenia showed a significant negative association with the cyclicity dimension ($p = 0.044$) but a significant positive association with the psychotic/irritable mania dimension ($p = 0.001$). PRS of EA major depressive disorder demonstrated a significant negative association with the elation dimension ($p = 0.003$) but a significant positive association with the comorbidity dimension ($p = 0.028$).

Conclusion. This study demonstrates that well-defined phenotype dimensions of lifetime-basis in BD have distinct genetic risks shared with other major mental illnesses. This finding supports genetic heterogeneity in BD and suggests a pleiotropy among BD subtypes and other psychiatric disorders beyond BD. Further genomic analyses adopting deep phenotyping across mental illnesses in ancestrally diverse populations are warranted to clarify intra-diagnosis heterogeneity and inter-diagnoses commonality issues in psychiatry.

Introduction

Bipolar disorder (BD) is a complex genetic disorder with high heritability (Smoller & Finn, 2003). Clinically, each patient shows unique (manic or depressive) episode symptoms with relapsing and remitting patterns (Nierenberg et al., 2023), which suggests a heterogeneity in its genetic basis. A significant portion of patients also demonstrate overlapping clinical features with other psychiatric diagnoses, such as schizophrenia, anxiety disorders, attention-deficit hyperactivity disorder (ADHD), and eating disorders (Mantere et al., 2010). This phenomenon has generated controversial issues regarding diagnostic boundaries and comorbidities. From a genomic perspective, it might reflect a pleiotropy among BD and other psychiatric illnesses (Lee, Feng, & Smoller, 2021; Stearns, 2010).

Several studies have sought genetically valid clinical subtypes of BD. In addition to bipolar 1 (BD-I) *v.* bipolar 2 (BD-II) subtyping, various clinical characteristics have been investigated in genome-wide studies (Coombes et al., 2020; Faraone, Su, & Tsuang, 2004; Kerner, Lambert, & Muthén, 2011; Labbe et al., 2012; Maciukiewicz et al., 2012, 2014; Meier et al., 2012; Monahan et al., 2015; Ruderfer et al., 2014). These studies have suggested different genetic basis for various subtypes. However, there is a lack of consistency in applied subtypes,

which limits the comparison between studies. In a previous study (Baek et al., 2019), the authors extracted six phenotype dimensions of BD from comprehensive lifetime clinical characteristics as possible homogenous phenotypes for genomic studies. Application of valid phenotypes would be an essential step to clarify the genetic architecture of complex genetic disorders.

In addition to genetic heterogeneity within single disorders, a strong possibility of pleiotropy, sharing common genomic risks among different illnesses, has been suggested in psychiatric disorders, including BD. Recent large-scale genome-wide association studies (GWAS) have consistently revealed genetic correlations among them (Frei et al., 2019; Kim et al., 2023; Lee et al., 2013). Given overlapping clinical features between BD and other psychiatric illnesses, certain subtypes of BD might share genes with other psychiatric disorders beyond just BD. To test this hypothesis, research designs incorporating intra-disease heterogeneity and inter-disease commonality into a single genomic analysis need to be applied.

In the present study, we attempted to test whether phenotypically heterogeneous subtypes of BD might have distinct polygenic risks that are shared with other psychiatric illnesses. We applied lifetime phenotype dimensions identified in our previous study (Baek et al., 2019) as BD subtypes. To investigate whether each phenotype dimension had a different association pattern with polygenic risks of major psychiatric illnesses, polygenic risk scores (PRSs) of six psychiatric illnesses from East Asian (EA) and other available populations were analyzed.

Methods

Study participants

A total of 467 patients with DSM-defined bipolar I (BD-I) or II disorder (BD-II) were recruited from Samsung Medical Center and Seoul National University Bundang Hospital. Of these participants included in the study, a total of 307 were included in our previous study, and 160 were additionally recruited. Basic demographic characteristics showed no significant difference between those who were included in our previous study and those who were later recruited in terms of basic demographic characteristics. Table 1 displays the basic demographic characteristics of the study participants.

Detailed recruitment and evaluation processes were described elsewhere (Baek et al., 2019). In brief, we recruited those with BD-I or BD-II who were clinically in stable conditions defined by the Clinical Global Impression of Severity scale score ⩽3. Written informed consent was obtained from all subjects after a complete explanation of the study. This study was also approved by the Institutional Review Boards at Samsung Medical Center and Seoul National University Bundang Hospital.

Table 1. Basic sociodemographic characteristics of study participants ($n = 467$)

Variables	
Age (mean [S.D.])	32.9 (11.0)
Sex, Male (n [%])	159 (34.0)
Bipolar type (n [%])	
Type I	252 (54.0)
Type II	215 (46.0)
Age at onset (mean [S.D.])	22.3 (8.9)
Duration of illness (months, mean [S.D.])	107.9 (86.9)
Currently married (n [%])	160 (34.3)
College graduate or more (n [%])	360 (77.1)

S.D., standard deviation.

Symptom dimension generation

The detailed process was described in our previous manuscript (Baek et al., 2019). In brief, clinical symptoms were assessed on a lifetime basis mainly through direct patient interviews using the Korean version of the Diagnostic Interview for Genetic Studies (DIGS) (Joo et al., 2004) or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (Han et al., 2000), using the DIGS at Samsung Medical Center or the SCID at Seoul National University Bundang Hospital. We selected 41 variables of lifetime characteristics of BD (including clinical course, seasonality, and chronotypes), symptom characteristics during acute episodes, and psychiatric comorbid conditions (six variables related to clinical courses, 29 variables covering lifetime symptoms of mood episodes, and 6 specific comorbid conditions) from the clinical data of 307 patients with BD. After conducting multiple imputations, iterative principal component analysis and varimax rotation were performed. Six factor models were selected based on scree plot acceleration factor rules, Velicer's minimum average partial test, and face validity evaluations. Variables with rotated factor loading <0.2 were excluded. As a result, a total of 37 phenotypes were included in phenotype dimension construction.

The six dimensions generated in our study were cyclicity, depression, atypical vegetative symptoms, elation, psychotic/irritable mania, and comorbidity dimensions. Detailed phenotypes included in each dimension are listed in online Supplementary Table S1.

In addition to phenotype dimension data from the original 307 participants used in phenotype dimension calculation, phenotype dimension scores of additional 160 participants were calculated using the same model. There was no significant difference in each dimension score between the initial samples used to develop the dimension model and those who were later included in the analysis.

Genotyping and imputation

The Korea Biobank Array (Moon et al., 2019) were used for genotyping DNA samples. We performed sample-level quality control (QC) and removed the indels before imputation. For the sample-level QC, the principal components of genetic ancestry were calculated using PLINK version 1.912 (Purcell et al., 2007) and used as covariates in the GWAS analysis. Two samples were removed after sample-level QC. Phasing and imputation were performed with Eagle v2.4 and Minimac 4 using the Korean Imputation Service Phase 1 reference panel with this set of shared single nucleotide variants (SNVs) (Hwang, Choi, Won, Kim, & Kim, 2022). After imputation, variants with an imputation quality of R^2 <0.80 or call rate <98% were removed. Finally, 9 556 467 SNVs were used for data analysis.

PRS construction

We constructed PRS using the PRS-CS method (Ge, Chen, Ni, Feng, & Smoller, 2019). We calculated PRSs for BD (PRS-BD)

https://doi.org/10.1017/S003329172400120X Published online by Cambridge University Press

and five mental illnesses (i.e. schizophrenia [SCZ], PRS-SCZ; major depressive disorder [MDD], PRS-MDD; obsessive-compulsive disorder [OCD], PRS-OCD; anxiety disorder [ANX], PRS-ANX; attention-deficit hyperactivity disorder [ADHD], PRS-ADHD) showing significant genetic correlations with BD in prior studies. PRSs for BD-I (PRS-BD-I) and BD-II (PRS-BD-II) were also separately calculated. As reference data, we used (1) the most recent and the largest GWAS and (2) GWAS with ancestrally appropriate populations. As there is limited availability of East Asian (EA) GWAS data, we could use summary data of EA GWASs for SCZ, BD, and MDD (PRS-SCZ-EA, PRS-BD-EA, and PRS-MDD-EA, respectively). For EA GWAS data of BD, we excluded Korean BD samples in order to avoid possible sample overlaps. Supplementary Table S2 shows information on reference data used to generate PRSs.

Statistical analyses

To explore associations of phenotype dimension scores with PRSs of six mental illnesses, linear regression analyses were conducted with each dimension score as a dependent variable and each PRS as an independent variable. Age, sex, and 10 principal component scores were entered as additional covariates. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.02.

Results

Table 2 displays the results of linear regression analyses using PRS from East Asian ancestry.

The cyclicity dimension showed a significant negative association with PRS-SCZ-EA ($\beta = -0.25$, $p = 0.044$), indicating BD patients with higher polygenic risk to SCZ had lower episode frequencies of manic and depressive episodes and less rapid cycling courses than those with lower polygenic risk to SCZ. In contrast, the psychotic/irritable mania dimension showed a significant positive association with the PRS-SCZ-EA ($\beta = 0.28$, $p = 0.001$), demonstrating patients with a higher genetic predisposition to SCZ presented with more psychotic and mixed features in their manic episodes.

The elation dimension revealed a significant negative association with PRS-MDD-EA ($\beta = -0.7$, $p = 0.003$). This reflects that patients having a higher score for this dimension with pure manic features of increased energy and elevated mood had lower polygenic risks for MDD. On the contrary, PRS-MDD-EA was significantly associated with the comorbidity dimension ($\beta = 0.28$, $p = 0.28$), indicating that BD patients with higher polygenic risk for MDD demonstrated diverse features of other psychiatric conditions such as anxiety disorders, eating disorders, and OCD.

Table 3 and Fig. 1 summarize the results of linear regression analyses using PRS from the largest GWAS generated with mixed ethnic groups. Supplementary Table S2 summarizes ancestry of the GWAS in detail. The psychotic/irritable mania dimension showed a similar positive association with PRS-SCZ ($\beta = 0.37$, $p < 0.001$) as with PRS-SCZ-EA. Additionally, a significant negative association was found between the depression dimension and PRS-SCZ ($\beta = -0.44$, $p = 0.031$). Unlike the analysis with East Asian PRS data, PRS-BD and PRS-BD-I ($\beta = 0.65$, $p = 0.03$; $\beta = 0.24$, $p = 0.007$, respectively) showed a significant association with the psychotic/irritable mania dimension score.

We did not find a significant association with any PRS score of other psychiatric disorders in the atypical vegetative symptoms

Table 2. Linear regression analyses on the association between polygenic risk score for mental illnesses from East Asian ancestry and six phenotype dimensions

	Phenotype dimension																	
	Depression			Cyclicity			Elation			Psychotic/irritable mania			Atypical vegetative symptoms			Comorbidity		
PRS	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2
SCZ-EA	−0.11 (−0.53 to 0.32)	0.624	0.03	**−0.25 (−0.49 to −0.01)**	**0.044**	**0.0563**	−0.06 (−0.24 to 0.12)	0.506	0.0347	**0.28 (0.11 to 0.44)**	**0.001**	**0.054**	0.13 (−0.04 to 0.3)	0.149	0.0696	0.02 (−0.08 to 0.12)	0.68	0.0607
BD-EA	−0.06 (−0.87 to 0.76)	0.892	0.033	0.01 (−0.46 to 0.48)	0.965	0.0478	−0.03 (−0.38 to 0.32)	0.863	0.0338	0.29 (−0.04 to 0.61)	0.085	0.0379	−0.06 (−0.39 to 0.27)	0.713	0.0656	−0.10 (−0.29 to 0.1)	0.325	0.0624
MDD-EA	−0.32 (−1.4 to 0.77)	0.568	0.0336	0.16 (−0.46 to 0.79)	0.61	0.0483	**−0.7 (−1.16 to −0.24)**	**0.003**	**0.0521**	0.15 (−0.28 to 0.59)	0.488	0.0326	0 (−0.44 to 0.44)	0.998	0.0653	**0.28 (0.03 to 0.54)**	**0.028**	**0.0703**

PRS, polygenic risk score; SCZ-EA, East Asian Schizophrenia; BD-EA, East Asian bipolar disorder; MDD-EA, East Asian major depressive disorder.
Dependent variable: each dimension score; independent variable: PRS for each mental illnesses stated on each row; age and sex were entered as covariates.
β value is presented with 95% confidence interval.
Bold font indicates statistical significance.

https://doi.org/10.1017/S003329172400120X Published online by Cambridge University Press

https://doi.org/10.1017/S003329172400120X Published online by Cambridge University Press

Table 3. Linear regression analyses on the association between polygenic risk score for mental illnesses from the largest available GWAS and six phenotype dimensions

	Phenotype dimension																	
	Depression			Cyclicity			Elation			Psychotic/irritable mania			Atypical vegetative symptoms			Comorbidity		
PRS	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2
SCZ	**−0.44 (−0.84 to −0.04)**	**0.031**	**0.0385**	−0.06 (−0.29 to 0.18)	0.637	0.0483	−0.05 (−0.22 to 0.12)	0.573	0.0345	**0.37 (0.22 to 0.53)**	**<0.001**	**0.0759**	0.07 (−0.09 to 0.24)	0.388	0.0669	0.07 (−0.03 to 0.16)	0.178	0.0641
BD	−1.26 (−2.74 to 0.22)	0.097	0.0388	0.22 (−0.64 to 1.08)	0.612	0.0483	0.14 (−0.5 to 0.78)	0.658	0.0342	**0.65 (0.06 to 1.24)**	**0.03**	**0.0415**	−0.34 (−0.95 to 0.26)	0.263	0.0679	0.02 (−0.33 to 0.37)	0.919	0.0604
BD-I	−0.12 (−0.57 to 0.32)	0.589	0.0335	0.02 (−0.23 to 0.28)	0.854	0.0479	0.1 (−0.09 to 0.29)	0.306	0.036	**0.24 (0.07 to 0.42)**	**0.007**	**0.0471**	0.05 (−0.13 to 0.24)	0.556	0.0661	−0.04 (−0.14 to 0.07)	0.465	0.0615
BD-II	0.11 (−0.34 to 0.56)	0.645	0.0334	0.05 (−0.21 to 0.31)	0.695	0.0481	0.09 (−0.0.1 to 0.29)	0.353	0.0356	0.08 (−0.1 to 0.26)	0.394	0.0331	0.01 (−0.17 to 0.19)	0.918	0.0654	−0.01 (−0.11 to 0.1)	0.901	0.0604
MDD	0.13 (−1.07 to 1.33)	0.832	0.033	0.55 (−0.15 to 1.24)	0.123	0.0528	−0.29 (−0.81 to 0.23)	0.27	0.0364	0.15 (−0.33 to 0.63)	0.541	0.0323	0.18 (−0.31 to 0.67)	0.475	0.0664	0.08 (−0.2 to 0.37)	0.568	0.061
ANX	−0.08 (−0.52 to 0.36)	0.718	0.0332	0.08 (−0.18 to 0.33)	0.551	0.0485	0.09 (−0.1 to 0.27)	0.373	0.0355	−0.15 (−0.32 to 0.03)	0.097	0.0374	0 (−0.18 to 0.18)	0.989	0.0653	0 (−0.11 to 0.1)	0.936	0.0604
OCD	0.17 (−0.07 to 0.41)	0.174	0.0325	0.07 (−0.07 to 0.21)	0.356	0.0496	−0.07 (−0.17 to 0.04)	0.222	0.037	0.04 (−0.06 to 0.13)	0.477	0.0326	0.04 (−0.05 to 0.14)	0.375	0.067	−0.01 (−0.06 to 0.05)	0.856	0.0604
ADHD	0.06 (−0.9 to 1.03)	0.902	0.0329	−0.15 (−0.71 to 0.4)	0.588	0.0484	0.2 (−0.22 to 0.61)	0.354	0.0356	−0.04 (−0.42 to 0.35)	0.857	0.0316	−0.35 (−0.74 to 0.04)	0.077	0.0718	−0.05 (−0.28 to 0.17)	0.646	0.0608

PRS, polygenic risk score; SCZ, schizophrenia; BD, bipolar disorder; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; MDD, major depressive disorder; ANX, anxiety disorder; OCD, obsessive-compulsive disorder; ADHD, attention deficit hyperactivity disorder.
Dependent variable: each dimension score; independent variable: PRS for each mental illnesses stated on each row; age and sex were entered as covariates.
β value is presented with 95% confidence interval.
Bold font indicates statistical significance.

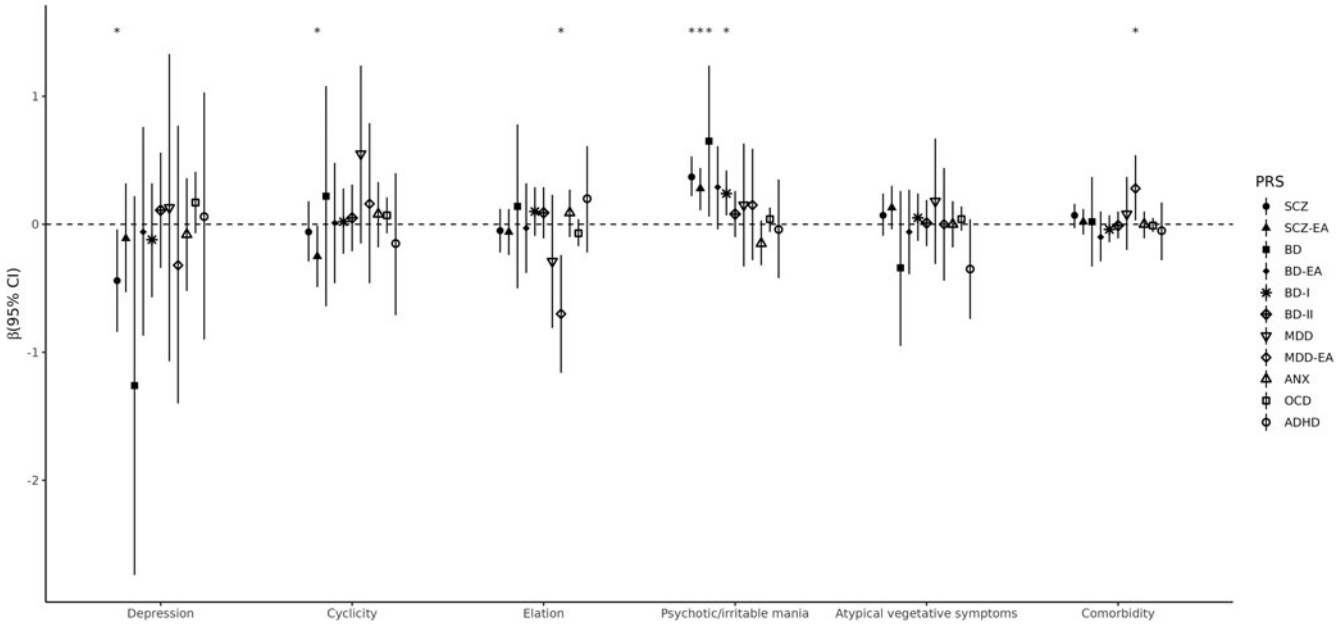

Figure 1. Comparisons of beta and 95% confidence interval from the linear regression analyses with polygenic risk score (PRS) for mental illnesses and six lifetime phenotype dimensions. The *X* axis denotes reference diagnosis of polygenic risk score; The *Y* axis denotes beta value. *p value <0.05. BD, bipolar disorder; BD-EA, East Asian bipolar disorder; BD-I, bipolar disorder type I; BD-II, bipolar disorder type II; SCZ, schizophrenia; SCZ-EA, East Asian schizophrenia; MDD, major depressive disorder; MDD-EA, East Asian major depressive disorder; OCD, obsessive compulsive disorder; ANX, anxiety disorder; ADHD, attention deficit hyperactivity disorder.

dimension. Also, PRS-BD-II, PRS-ANX, PRS-OCD, and PRS-ADHD were not associated with any phenotype dimension.

Figure 1 summarizes the beta values of PRSs in each phenotype dimension. PRSs generated using EA samples generally showed the same directions (plus *v.* minus) of beta values as PRSs generated using other ethnic samples. Also, analyses using EA samples identified the association quite efficiently despite much smaller sample sizes compared to the largest available GWAS data.

Discussion

The present study demonstrates that phenotype dimensions of BD created using the lifetime clinical characteristics have distinct genomic risk sharing with other mental disorders. This result supports clinical and genetic heterogeneity in BD. At the same time, it suggests the possibility that polygenic overlap between psychiatric illnesses, i.e., inter-diagnoses commonality or pleiotropy, could be identified at the level of specific phenotype dimensions across diagnostic boundaries.

In exploring the genetic basis of psychiatric illnesses, within-diagnosis heterogeneity and inter-diagnoses commonality have been regarded as an important issue to be clarified. Genomic data for various endophenotypes and subtypes within single diseases have been accumulated (Guglielmo, Miskowiak, & Hasler, 2021). Also, recent genomic studies started to reveal significant inter-disease correlations between psychiatric illnesses (Docherty et al., 2023). However, research questions or designs incorporating the two issues into a single study have yet to be attempted much. For this approach, BD is an optimal complex genetic disorder, given its diversity in clinical manifestation and highly overlapping clinical features with other psychiatric illnesses, such as psychotic disorders, anxiety disorders, ADHD, eating disorders, and substance abuse (Nierenberg et al., 2023).

The application of deep phenotyping in genomic studies for BD has been tried only recently. So, a direct comparison of the current results with previous studies might be difficult. However, our study findings are in line with several prior study results with similar research questions.

The PRS-SCZ and PRS-SCZ-EA both showed significant positive associations with the psychotic/irritable mania dimension. This result is consistent with European study findings demonstrating associations between psychosis dimensions in BD and PRS-SCZ (Coombes et al., 2020; Markota et al., 2018). In a study that generated phenotype dimensions across SCZ, BD, and MDD, the psychotic feature was also associated with PRS-SCZ (David et al., 2023). Together with these findings, the current result suggests that psychotic, irritable, and mixed features of mania might be a phenotypic constellation sharing the genetic risk with SCZ.

In contrast, the cyclicity dimension showed a significant negative association with PRS-SCZ-EA. This suggests that BD patients with more genetic predisposition for SCZ are less likely to show high cyclicity in their illness courses. In our previous study, the cyclicity dimensions were significantly more presented in BD-II compared to BD-I (Baek et al., 2019). It might be compatible with recent genomic study findings showing a higher genetic correlation with SCZ in BD-I than in BD-II (Li, Li, & Chen, 2022).

In the present study, PRS-MDD-EA demonstrated a significant negative association with the elation dimension (p = 0.003). Subjects with high scores in this dimension would present higher and more dominant manic features. Therefore, the negative correlation of this dimension with PRS-MDD-EA suggests that genetic loci contributing to the development of MDD might have a symptom- or course-modifying role in BD.

Regarding the comorbidity dimension, the term 'comorbidity' might be a misnomer. Though our previous and current studies used this term, this dimension could, in fact, reflect miscellaneous BD features overlapping with eating disorders, anxiety disorders,

https://doi.org/10.1017/S003329172400120X Published online by Cambridge University Press

and OCD. A significant association of this dimension with PRS-MDD-EA might be compatible with the high prevalence of anxiety, obsessive-compulsive, and eating disorder symptoms in MDD (Kessler et al., 2008; Overbeek, Schruers, Vermetten, & Griez, 2002; Welch et al., 2016). Depression is also known as having intricate genetic architecture (Flint & Kendler, 2014) with high genetic heterogeneity. It would be worthwhile to evaluate the association between this dimension and PRS for eating disorders, anxiety disorders, and OCD. However, we could not find reference GWAS data on EA populations for those diagnoses. We tried to use European data, which showed no significant correlations. Of note, a prior European study indicated a noteworthy association between comorbid ANX in BD and PRS-ANX (Lopes et al., 2020).

The atypical vegetative symptoms dimension did not show any significant associations with PRS examined in our study. Notably, this dimension was quite independent, not showing any significant association with other dimensions in our previous study (Baek et al., 2019). In a recent study with UK biobank data, atypical depression showed a significant positive association with PRS for immune-metabolic traits compared to non-atypical depression (Badini et al., 2022).

This study highlights the need for establishing genomic data sets of diverse ancestral origins. Analysis using European reference data did not show the same results as those using EA reference data (Table 2, Table 3). For BD-I and BD-II subtypes, anxiety disorders, OCD, and ADHD, East Asian populations GWAS data with sufficient sample sizes were not available. Also, there were no Korean GWAS data to be used as reference data for the current analysis.

Our study findings have several limitations. First, the sample size of the subjects might not be enough to examine heterogenous phenotype dimensions. Second, as mentioned previously, limited large-scale GWAS data from East Asian or Korean populations could also affect the study findings. In particular, large-scale GWAS for Korean patients with mental illnesses were not available. Third, despite significant associations observed in our study, the amount of variance explained using PRS was still small. Lastly, we did not have validation samples.

Notwithstanding these limitations, this study provided insight into how intra-diagnosis heterogeneity and inter-diagnoses commonality issues can be integrated in understanding genetic basis of psychiatric disorders. The strength of this study is a deep phenotyping and dimensional approach in defining phenotypes. In future genomic studies, deep phenotyping across psychiatric illnesses beyond diagnostic boundaries is required for diverse ancestral populations. Through these efforts, we will be able to approach closer to the goal of biology-based reclassification of mental illnesses.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172400120X.

Acknowledgements. We would like to thank Jinseob Kim (Zarathu Co., Ltd., Seoul, Republic of Korea) for statistical advice.

Authors' contributions. JHB and KSH designed the overall study and generated the hypothesis. JHB, THH, KH, and HKS participated in participant recruitment. HWJ took part in data collection. EYC collected genomic samples and took part in the genomic analysis part. DL conducted statistical analyses. JHB wrote the manuscript. All authors took part in the final manuscript editing process.

Funding statement. This study was supported by the Original Technology Research Program for Brain Science through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (grant number: NRF-2019M3C7A1030624).

Competing interests. The authors have no relevant financial or non-financial interests to disclose.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Badini, I., Coleman, J. R. I., Hagenaars, S. P., Hotopf, M., Breen, G., Lewis, C. M., & Fabbri, C. (2022). Depression with atypical neurovegetative symptoms shares genetic predisposition with immuno-metabolic traits and alcohol consumption. *Psychological Medicine*, *52*(4), 726–736. doi: 10.1017/s0033291720002342

Baek, J. H., Ha, K., Kim, Y., Cho, Y. A., Yang, S. Y., Choi, Y., … Hong, K. S. (2019). Psychopathologic structure of bipolar disorders: Exploring dimensional phenotypes, their relationships, and their associations with bipolar I and II disorders. *Psychological Medicine*, *49*(13), 2177–2185. doi: 10.1017/s003329171800301x

Coombes, B. J., Markota, M., Mann, J. J., Colby, C., Stahl, E., Talati, A., … Biernacka, J. M. (2020). Dissecting clinical heterogeneity of bipolar disorder using multiple polygenic risk scores. *Translational Psychiatry*, *10*(1), 314. doi: 10.1038/s41398-020-00996-y

David, F. S., Stein, F., Andlauer, T. F. M., Streit, F., Witt, S. H., Herms, S., … Forstner, A. J. (2023). Genetic contributions to transdiagnostic symptom dimensions in patients with major depressive disorder, bipolar disorder, and schizophrenia spectrum disorders. *Schizophrenia Research*, *252*, 161–171. doi: 10.1016/j.schres.2023.01.002

Docherty, A. R., Mullins, N., Ashley-Koch, A. E., Qin, X., Coleman, J. R. I., Shabalin, A., … Ruderfer, D. M. (2023). GWAS Meta-analysis of suicide attempt: Identification of 12 genome-wide significant loci and implication of genetic risks for specific health factors. *American Journal of Psychiatry*, *180*(10), 723–738. doi: 10.1176/appi.ajp.21121266

Faraone, S. V., Su, J., & Tsuang, M. T. (2004). A genome-wide scan of symptom dimensions in bipolar disorder pedigrees of adult probands. *Journal of Affective Disorders*, *82* (Suppl 1), S71–S78. doi: 10.1016/j.jad.2004.05.015

Flint, J., & Kendler, K. S. (2014). The genetics of major depression. *Neuron*, *81*(3), 484–503. doi: 10.1016/j.neuron.2014.01.027

Frei, O., Holland, D., Smeland, O. B., Shadrin, A. A., Fan, C. C., Maeland, S., … Dale, A. M. (2019). Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. *Nature Communications*, *10*(1), 2417. doi: 10.1038/s41467-019-10310-0

Ge, T., Chen, C. Y., Ni, Y., Feng, Y. A., & Smoller, J. W. (2019). Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nature Communications*, *10*(1), 1776. doi: 10.1038/s41467-019-09718-5

Guglielmo, R., Miskowiak, K. W., & Hasler, G. (2021). Evaluating endophenotypes for bipolar disorder. *International Journal of Bipolar Disorders*, *9*(1), 17. doi: 10.1186/s40345-021-00220-w

Han, O., Ahn, S., Siong, M., Cho, J., Kim, J., Bae, S., … Park, J. (2000). Development of Korean version of structured clinical interview schedule for DSM-IV axis I disorder: Interrater reliability. *Journal of Korean Neuropsychiatric Association*, *39*, 362–372.

Hwang, M. Y., Choi, N. H., Won, H. H., Kim, B. J., & Kim, Y. J. (2022). Analyzing the Korean reference genome with meta-imputation increased the imputation accuracy and spectrum of rare variants in the Korean population. *Frontiers in Genetics*, *13*, 1008646. doi: 10.3389/fgene.2022.1008646

Joo, E. J., Joo, Y. H., Hong, J. P., Hwang, S., Maeng, S. J., Han, J. H., … Kim, Y. S. (2004). Korean Version of the diagnostic interview for genetic studies: Validity and reliability. *Comprehensive Psychiatry*, *45*(3), 225–229. doi: 10.1016/j.comppsych.2004.02.007

Kerner, B., Lambert, C. G., & Muthén, B. O. (2011). Genome-wide association study in bipolar patients stratified by co-morbidity. *PLoS ONE*, *6*(12), e28477. doi: 10.1371/journal.pone.0028477

Kessler, R. C., Gruber, M., Hettema, J. M., Hwang, I., Sampson, N., & Yonkers, K. A. (2008). Co-morbid major depression and generalized anxiety

disorders in the national comorbidity survey follow-up. *Psychological Medicine*, *38*(3), 365–374. doi: 10.1017/s0033291707002012

Kim, H. K., Gonçalves, V. F., Husain, M. I., Müller, D. J., Mulsant, B. H., Zai, G., & Kloiber, S. (2023). Cross-disorder GWAS meta-analysis of endocannabinoid DNA variations in major depressive disorder, bipolar disorder, attention deficit hyperactivity disorder, autism spectrum disorder, and schizophrenia. *Psychiatry Research*, *330*, 115563. doi: 10.1016/j.psychres.2023.115563

Labbe, A., Bureau, A., Moreau, I., Roy, M. A., Chagnon, Y., Maziade, M., & Merette, C. (2012). Symptom dimensions as alternative phenotypes to address genetic heterogeneity in schizophrenia and bipolar disorder. *European Journal of Human Genetics*, *20*(11), 1182–1188. doi: 10.1038/ejhg.2012.67

Lee, P. H., Feng, Y. A., & Smoller, J. W. (2021). Pleiotropy and cross-disorder genetics among psychiatric disorders. *Biological Psychiatry*, *89*(1), 20–31. doi: 10.1016/j.biopsych.2020.09.026

Lee, S. H., Ripke, S., Neale, B. M., Faraone, S. V., Purcell, S. M., Perlis, R. H., … Wray, N. R. (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics*, *45*(9), 984–994. doi: 10.1038/ng.2711

Li, Z., Li, D., & Chen, X. (2022). Characterizing the polygenic overlaps of bipolar disorder subtypes with schizophrenia and major depressive disorder. *Journal of Affective Disorders*, *309*, 242–251. doi: 10.1016/j.jad.2022.04.097

Lopes, F. L., Zhu, K., Purves, K. L., Song, C., Ahn, K., Hou, L., … McMahon, F. J. (2020). Polygenic risk for anxiety influences anxiety comorbidity and suicidal behavior in bipolar disorder. *Translational Psychiatry*, *10*(1), 298. doi: 10.1038/s41398-020-00981-5

Maciukiewicz, M., Czerski, P. M., Leszczynska-Rodziewicz, A., Kapelski, P., Szczepankiewicz, A., Dmitrzak-Weglarz, M., … Karlowski, W. M. (2012). Analysis of OPCRIT results indicate the presence of a novel 'social functioning' domain and complex structure of other dimensions in the Wielkopolska (Poland) population. *Schizophrenia Research*, *138*(2-3), 223–232. doi: 10.1016/j.schres.2012.03.032

Maciukiewicz, M., Dmitrzak-Weglarz, M., Pawlak, J., Leszczynska-Rodziewicz, A., Zaremba, D., Skibinska, M., & Hauser, J. (2014). Analysis of genetic association and epistasis interactions between circadian clock genes and symptom dimensions of bipolar affective disorder. *Chronobiology International*, *31*(6), 770–778. doi: 10.3109/07420528.2014.899244

Mantere, O., Isometsä, E., Ketokivi, M., Kiviruusu, O., Suominen, K., Valtonen, H. M., … Leppämäki, S. (2010). A prospective latent analyses study of psychiatric comorbidity of DSM-IV bipolar I and II disorders. *Bipolar Disorder*, *12*(3), 271–284. doi: 10.1111/j.1399-5618.2010.00810.x

Markota, M., Coombes, B. J., Larrabee, B. R., McElroy, S. L., Bond, D. J., Veldic, M., … Biernacka, J. M. (2018). Association of schizophrenia polygenic risk score with manic and depressive psychosis in bipolar disorder. *Translational Psychiatry*, *8*(1), 188. doi: 10.1038/s41398-018-0242-3

Meier, S., Mattheisen, M., Vassos, E., Strohmaier, J., Treutlein, J., Josef, F., … Szelinger, S. (2012). Genome-wide significant association between a 'negative mood delusions' dimension in bipolar disorder and genetic variation on chromosome 3q26.1. *Translational Psychiatry*, *2*(9), e165. doi: 10.1038/tp.2012.81

Monahan, P. O., Stump, T., Coryell, W. H., Harezlak, J., Marcoulides, G. A., Liu, H., … Nurnberger, J. I. (2015). Confirmatory test of two factors and four subtypes of bipolar disorder based on lifetime psychiatric co-morbidity. *Psychological Medicine*, *45*(10), 2181–2196. doi: 10.1017/s0033291715000185

Moon, S., Kim, Y. J., Han, S., Hwang, M. Y., Shin, D. M., Park, M. Y., … Kim, B. J. (2019). The Korea biobank array: Design and identification of coding variants associated with blood biochemical traits. *Scientific Reports*, *9*(1), 1382. doi: 10.1038/s41598-018-37832-9

Nierenberg, A. A., Agustini, B., Kohler-Forsberg, O., Cusin, C., Katz, D., Sylvia, L. G., … Berk, M. (2023). Diagnosis and treatment of bipolar disorder: A review. *JAMA*, *330*(14), 1370–1380. doi: 10.1001/jama.2023.18588

Overbeek, T., Schruers, K., Vermetten, E., & Griez, E. (2002). Comorbidity of obsessive-compulsive disorder and depression: Prevalence, symptom severity, and treatment effect. *Journal of Clinical Psychiatry*, *63*(12), 1106–1112. doi: 10.4088/jcp.v63n1204

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., … Sham, P. C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*, *81*(3), 559–575. doi: 10.1086/519795

Ruderfer, D. M., Fanous, A. H., Ripke, S., McQuillin, A., Amdur, R. L., Gejman, P. V., … Kendler, K. S. (2014). Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Molecular Psychiatry*, *19*(9), 1017–1024. doi: 10.1038/mp.2013.138

Smoller, J. W., & Finn, C. T. (2003). Family, twin, and adoption studies of bipolar disorder. *American Journal of Medical Genetics. Part C: Seminars in Medical Genetics*, *123c*(1), 48–58. doi: 10.1002/ajmg.c.20013

Stearns, F. W. (2010). One hundred years of pleiotropy: A retrospective. *Genetics*, *186*(3), 767–773. doi: 10.1534/genetics.110.122549

Welch, E., Jangmo, A., Thornton, L. M., Norring, C., von Hausswolff-Juhlin, Y., Herman, B. K., … Bulik, C. M. (2016). Treatment-seeking patients with binge-eating disorder in the Swedish national registers: Clinical course and psychiatric comorbidity. *BMC Psychiatry*, *16*, 163. doi: 10.1186/s12888-016-0840-7

https://doi.org/10.1017/S003329172400120X Published online by Cambridge University Press