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Original Article

Using multi-trait polygenic scores to predict lithium responsiveness in patients with bipolar disorder

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Background

The predictive power of polygenic scores (PGSs) for lithium treatment response in bipolar disorder remains limited.

Aims

To enhance the prediction of lithium responsiveness by developing a multi-trait PGS (mt-PGS) combining genetic information from multiple phenotypes implicated in lithium response and/or bipolar disorder aetiology.

Method

We analysed data collected from bipolar disorder patients who had received lithium treatment for at least 6 months and participated in the International Consortium on Lithium Genetics study ($N = 2367$). The Alda scale was used to assess lithium responsiveness, and treatment outcome was defined as continuous total Alda score (0–10) and categorical outcome (favourable ≥ 7 versus unfavourable response). PGSs were calculated for 60 phenotypes grouped into 5 clinical–biological clusters: psychiatric and behavioural (#23 phenotypes), cardiometabolic (#17), autoimmune/inflammatory (#5), neurocognitive (#8) and renal function (#7). We applied cross-validated machine learning regression approaches in both outcomes within each cluster, with the selected features from each cluster subsequently combined to construct the final mt-PGS models. Model performance was assessed using explained variance (R^2) for the continuous outcome, and both McFadden's pseudo-R^2 and standard classification model parameters for the categorical outcome.

Results

mt-PGS explained between 5.70% (continuous outcome) and 9.11% (categorical outcome) of the interindividual variability in lithium responsiveness. Classification accuracy (area under the curve) for the categorical outcome was 68.24% (95% CI: 64.98–71.66), with a Brier score of 0.257. Of the 5 clusters, the PGSs for psychiatric and behavioural phenotypes were most strongly associated with lithium responsiveness, accounting for 3.67–6.52% of its variability.

Conclusions

By integrating PGSs for multiple relevant phenotypes, predictive accuracy for lithium response improved substantially compared with single-trait methods. Future research incorporating larger, more diverse populations and combining genetic scores with clinical data holds promise for further enhancing prediction and advancing clinical implementation.

Keywords

Lithium; polygenic score; pharmacogenomics; machine learning; psychiatry.

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Bipolar disorder is one of the most severe and prevalent mental illnesses, affecting about 40 to 50 million people worldwide[1] and with an estimated 15–20% dying by suicide.[2] It is a complex disorder characterised by recurrent hypomanic or manic and depressive episodes and is associated with significant somatic and psychiatric comorbidity.[3] Lithium has remained the gold standard and first-line medication for patients with bipolar disorder for over 70 years,[4,5] effectively treating acute episodes of illness, preventing relapses and demonstrating anti-suicidal properties.[6,7] However, not all bipolar disorder patients experience sustained clinical benefits. Studies indicate that only about 30% of patients achieve full clinical remission with lithium monotherapy whereas 30–40% exhibit minimal clinical response.[8,9] Clinical causes and predictors of this response heterogeneity have been identified and summarised into a 'clinical exemplar' for optimal lithium response.[10,11] Nevertheless, these clinical variables alone do not fully explain interindividual variability,[12] and in practice are difficult to comprehensively elicit from patients at the point of treatment decision. Therefore, the field has pursued the search for an objective biological predictor for the lithium-responsive phenotype that could support both clinicians and patients in their decision-making.

Previous studies have developed polygenic scores (PGSs) to predict lithium responsiveness in bipolar disorder, focusing on genetic risk profiles for related psychiatric conditions such as schizophrenia (SCZ),[13] major depressive disorders (MDD)[14] attention-deficit hyperactivity disorder (ADHD)[15] and on the lithium-responsiveness phenotype itself.[16,17] Although these PGSs have shown statistically significant associations with lithium treatment outcomes, each individual PGS explains only a small portion of the variability in lithium response – typically between 0.18 and 2.60%, indicating limited clinical utility when used alone.[18–20]

An emerging approach to improving predictive accuracy is integrating PGSs for multiple phenotypes that share genetic architecture with the phenotype of interest. For example, Schubert et al meta-analysed the PGSs for MDD and SCZ and found a twofold increase in predictive capability compared with single-trait PGSs.[21] Another study by Albinana and colleagues combined 937 PGSs derived from multiple diseases and conditions that enhanced predictive accuracy for psychiatric diagnoses such as ADHD, affective disorder, autism spectrum disorder, bipolar disorder, anorexia nervosa and SCZ. Using this methodology, the explained variance for each diagnosis was four- to ninefold larger compared with a single-disorder PGS.[22] Similarly, Krapohl et al used 81 Genome-Wide Association Studies (GWAS) of cognitive, medical and anthropometric phenotypes to predict educational achievement, general cognitive ability and body mass index (BMI). They found that the combined PGSs predicted 10.9% variance in educational achievement, 4.8% in general cognitive ability and 5.4% in BMI – representing increases of 10, 10 and 60%, respectively, compared with the best-performing single-score predictions.[23] These examples highlight the potential value of harnessing the shared genetic architecture of multiple phenotypes to improve the predictive power of PGSs for complex traits such as lithium response in bipolar disorder.

Aims

In the current study, we applied supervised machine learning methods within a multi-trait PGS (mt-PGS) framework to predict lithium responsiveness in patients with bipolar disorder. By integrating PGSs from multiple phenotypes previously implicated in bipolar disorder pharmacology and/or aetiology, we evaluated whether the mt-PGS approach would improve predictive performance. Additionally, we explored the relative contribution of each phenotype-specific PGS to lithium response, providing insights into its genetic relationship with lithium response phenotype.

Method

This study adheres to the Transparent Reporting of a multivariable Prediction model for Individual Prognosis Or Diagnosis – Artificial Intelligence (TRIPOD-AI) guideline[24] to report the findings. The completed TRIPOD-AI checklist is provided in the supplementary material.

Data source and patient population

We utilised data from the International Consortium on Lithium Genetics (ConLi^{+}Gen; http://www.conligen.org/), a global initiative investigating the genetic basis of lithium response in bipolar disorder. For this analysis, we included 2367 patients of European ancestry who received lithium and were followed up for a minimum of 6 months. Participants were recruited from Europe, North America, Asia and Australia between 2008 and 2013.[25] Detailed characteristics of this cohort, including clinical and demographic information, are available elsewhere.[9]

Target outcome measure

The Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder score (Alda scale), a validated retrospective criteria of long-term treatment response in research subjects, was used to assess patients' response to lithium treatment.[26,27] This scale quantifies the degree of improvement during lithium therapy by combining changes in the frequency and severity of mood symptoms into an A score (ranging from 0 to 10). To account for potential confounding factors influencing symptom improvement, the scale also incorporates a B score that considers five confounders, each scored 0, 1 or 2. The total score is then derived by subtracting the total B score from the A score. The detailed procedures for Alda scale measurement are described elsewhere.[26,27] For this study, lithium treatment outcome was defined both as a continuous outcome (Alda score) and a categorical outcome, with those patients having a total score of 7 or higher classified as 'favourable responders' and those with a score less than 7 classified as 'unfavourable responders'.[9,27]

An overview of the steps involved in developing mt-PGS and the data analysis procedures is outlined in Fig. 1.

Step 1: Selection of phenotypes

For this study, we selected 60 phenotypes previously implicated in and/or potentially sharing a genetic architecture with the pharmacology or aetiology of bipolar disorder. The included phenotypes comprised psychiatric disorders and clinical–behavioural traits,[28] cardiometabolic traits,[29] cognitive functions,[30] autoimmune and inflammatory conditions[31] and renal function biomarkers.[32] Details of the phenotype screening process, and a narrative review showing the biological and clinical implications of each phenotype for

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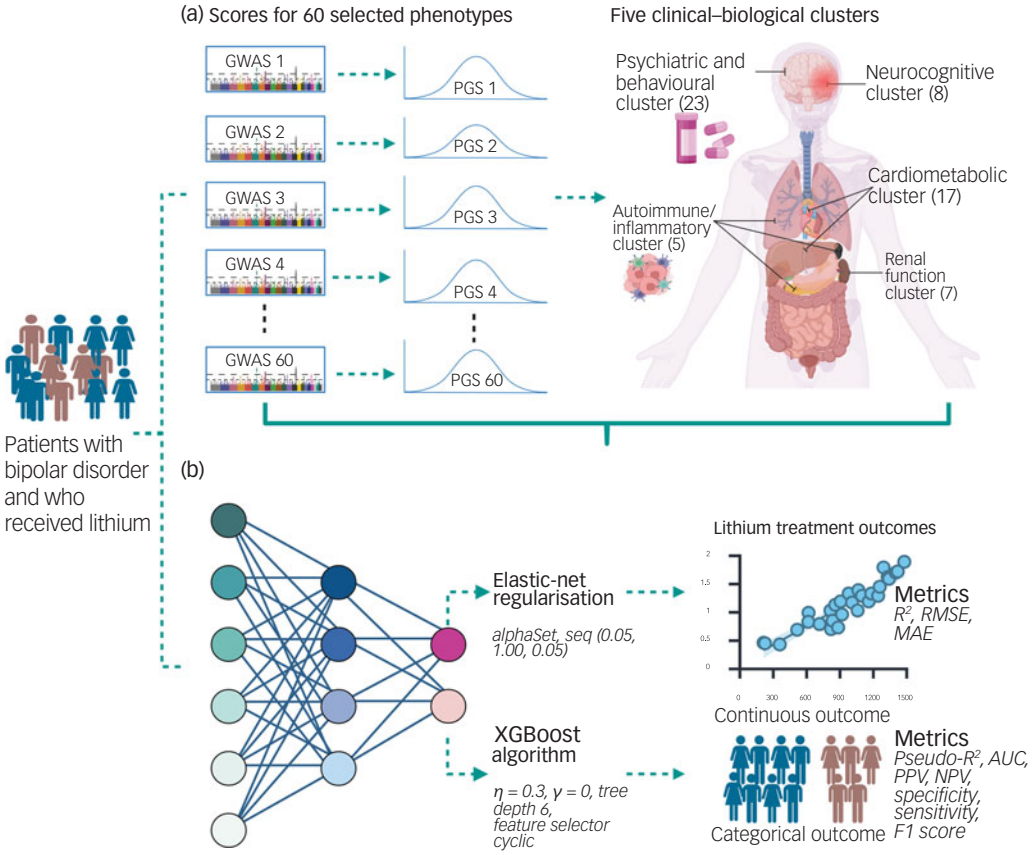


Fig. 1 The detailed steps for developing mt-PGS and data analysis procedures. (a) Polygenic score development and feature clustering. (b) Supervised machine learning modelling. mt-PGS, multi-trait polygenic score; GWAS, Genome-Wide Association Study; PGS, polygenic score; XGBoost, extreme gradient-boosted decision tree-based ensembles; R^2, explained variance; RMSE, root mean squared error; MAE, mean absolute error; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

bipolar disorder pharmacology or aetiology, are provided in the Supplementary Methods. Briefly, the selection process involved downloading all available GWASs reported in the GWAS catalogue and other databases, resulting in 63 967 GWAS summary statistics across 12 767 phenotypes as of 26 April 2024. We excluded phenotypes derived from multi-omics studies, including proteomic, metabolomic and lipidomic, as well as blood cell measurement and rare copy variants-based GWAS. Phenotypes from studies conducted in non-European ancestries and those with limited clinical relevance to bipolar disorder pharmacology or aetiology were also excluded. Finally, 60 phenotypes that appeared in the narrative review and had corresponding GWAS summary data were considered for the final analyses. We provide Supplementary Fig. 1 showing the screening process of phenotypes from the GWAS catalogue and other databases.

Step 2: Computing PGSs and building a mt-PGS library

To develop PGSs, we extracted publicly available summary statistics (discovery data) for the selected phenotypes from the GWAS catalogue (https://www.ebi.ac.uk/gwas/), GWAS Atlas (https://atlas.ctglab.nl/), GIANT consortium (https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium), CNCR – CTG lab (https://cncr.nl/ctg/) and Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc). Detailed characteristics of the GWAS summary statistics used are provided in Supplementary Table 2.

Before developing the PGSs, genotype data from the ConLi$^+$Gen consortium (target sample) underwent standard quality control and imputation procedures, as previously described.[9,13,14,17,21] A brief summary of the genotyping, quality control and imputation steps is provided in Supplementary Methods.

Using the GWAS summary statistics described above, the quality control-filtered individuals and single-nucleotide proteins from the ConLi$^+$Gen sample and the precomputed linkage disequilibrium of the 1000 Genome European external reference panel, PGSs for each phenotype were computed. The polygenic risk score–continuous shrinkage scoring method was employed to construct the PGS for each phenotype.[33] Subsequently, we constructed an agnostic PGS library for the selected phenotypes. Each score was standardised to a zero mean and unit variance. Detailed information on the computation of PGSs is available in Supplementary Methods.

Step 3: Phenotype clustering for dimensionality reduction

Because the number of features in this study (#60) was large relative to the sample size, a clustering strategy was implemented for dimensionality reduction. The numbers of clusters and cluster labels were assigned following expert consultation involving two psychiatrists and one genetic epidemiologist. These experts also independently reviewed and confirmed the assignment of each phenotype to the respective clusters (Supplementary Table 3). Accordingly, the phenotypes were grouped into five clinically and biologically informed clusters: *psychiatric disorders and clinical–behavioural phenotypes (or 'psychiatric and behavioural') (#23), cardiometabolic (#17), autoimmune/inflammatory (#5), neurocognitive (#8) and renal function (#7)* (Supplementary Table 4).

The optimal number of features per cluster was determined using the R package *pmsampsize*,[34] which indicated that clusters

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containing approximately 10–18 features were appropriate for the available sample size (Supplementary Methods).

Step 4: Developing mt-PGS using machine learning models

We trained an elastic-net regression for the continuous outcome and extreme gradient-boosted decision tree-based ensembles (XGBoost) for the categorical outcome using fivefold nested cross-validation within each cluster. Our data-set was partitioned into inner-loop training folds (80%, $N = 1894$) and an outer-loop testing fold (20%, $N = 473$). The inner and outer loops were independent, and prediction scores and performance metrics were aggregated across all outer-loop folds. The inner folds were used to tune hyperparameters and minimise cross-validation error, while the model was trained on the entire inner training set and evaluated on omitted data from the outer fold. This procedure was repeated for each outer fold, after which the pooled predictions from unseen test data were compared against the ground-truth outcomes.[35] Features retained from the cluster-level analysis were then combined for the final mt-PGS analysis. A step-by-step analysis procedure for developing mt-PGS models is available in Supplementary Methods, and the flow diagram is shown in Supplementary Fig. 2. Detailed modelling procedures for each outcome are described below.

Continuous outcome model (A)

Elastic-net regularisation regression was employed because of the substantial genetic correlations among selected predictors within and across clusters in our data. By blending the penalties of ridge and LASSO regression, elastic-net effectively handles correlated predictors while simultaneously performing feature selection, thereby improving model stability, predictive performance and interpretability compared with either method alone.[35–37] We used 5 inner folds and evaluated a hyperparameter range of 0.05 to 1.00 with steps of 0.05 for the regularisation strength parameter (α). Details of the hyperparameter space are provided in Supplementary Table 1. The predictive performance of models was assessed using R^2, root mean squared error (RMSE) and mean absolute error (MAE) for each cluster and the final mt-PGS models. We ranked the contribution of features to the continuous outcome based on their absolute standardised coefficient in the final mt-PGS model.

Categorical outcome model (B)

The XGBoost algorithm was selected for the categorical outcome due to its remarkable accuracy and adaptability, by capturing complex, non-linear relationships and correlations among predictors through sequential gradient-boosting that iteratively learns from previous prediction errors.[38,39] In addition, the algorithm can accommodate class imbalance through class-weighting, making it suitable for our data-set, which comprised 660 responders and 1707 non-responders to lithium treatment.[40] Furthermore, feature importance was evaluated using Shapley additive explanation (SHAP) values, which quantify the contribution of each predictor to the model output and identify the most important polygenic predictors.[41] XGBoost has also demonstrated robust predictive performance across a range of biomedical applications, including psychiatric genetics and mood disorder classification, where it has frequently outperformed conventional machine learning approaches in capturing complex disease architectures.[42,43] A learning rate (η) of 0.3, a minimum loss reduction (Υ, Lagrangian multiplier) of 0, a maximum tree depth of 6 and cyclic feature selector hyperparameter spaces were applied (see Supplementary Table 1 for further details on the hyperparameter space). Model discrimination, the accuracy of classification models, was evaluated using area under the curve (AUC), balanced accuracy, accuracy, negative and positive predictive values, sensitivity, specificity and F1 score. Model calibration was evaluated for the classification models using out-of-fold predicted probabilities obtained from the outer loop of nested cross-validation. Predicted probabilities were truncated to the interval 1.0×10^{-6} to $1.0 - (1 \times 10^{-6})$, prior to logit transformation to avoid numerical instability. Overall calibration performance was assessed using the Brier score, which quantifies the proximity of predicted probabilities to observed outcomes; this score ranges from 0 to 1, where lower values indicate superior model performance. Additionally, bootstrap bias-corrected calibration curves were plotted to examine agreement between predicted and observed probabilities.[44] The R package 'boost' was used to bootstrap a 95% confidence interval for prediction performance metrics with 500 bootstrap replicates and the 'perc' method. Class weights were applied based on the ratio of responders and non-responders to achieve balanced predictions for imbalanced data, and to assign greater importance to misclassifications of the underrepresented class during optimisation. McFadden pseudo-R^2 was calculated and the reported observed R^2 was transformed to a liability scale,[45] taking into account a lithium responsiveness prevalence of 30%[9] and the proportion of lithium responders to non-responders in the target cohort. Finally, the importance of features was ranked using the mean SHAP value, which determines the contribution of each feature to the categorical outcome in the final mt-PGS model. The SHAP value is the average marginal contribution of a feature value across all possible coalitions in the XGBoost models.[41]

All machine learning analyses were conducted in R version 4.3.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/) using the Caret package version 6.0-94 for Windows (Max Kuhn et al; https://cran.r-project.org/package=caret).

Ethical standards

The Ethics Committee at the University of Heidelberg provided central ethical approval for the consortium, and written consent was obtained from all participants according to the study protocols of each of the participating sites and their institutions. All procedures were performed according to the Declaration of Helsinki guidelines.[9]

Results

Cohort characteristics

A total of 2367 patients with bipolar disorder who had been treated with lithium for at least 6 months were included in this study. Nearly 60% of participants were female and mean age was 47.53 ± 13.73 years. Of the total sample, 660 patients (27.9%) responded favourably to lithium treatment and the mean Alda total score was 4.12 ± 3.15. Detailed sample characteristics of the cohort can be found in previous publications[9,13,14,17,21] and in Table 1.

Polygenic scores derived from 60 phenotypes were analysed. Pairwise genetic correlation (rg) analyses across these 1770 phenotype pairs showed 409 statistically significant positive correlations and 263 statistically significant negative correlations ($p < 0.05$). Full genetic correlation results are shown in Supplementary Table 5, with a heatmap of phenotypes in the final models presented in Supplementary Fig. 3.

Multi-trait polygenic model for lithium response (continuous outcome)

The final mt-PGS model combining PGSs from 25 phenotypes across 5 clusters explained 5.70% of the variance in lithium responsiveness (RMSE = 3.26, MAE = 2.84; see Table 2 for full

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Table 1 Characteristics of the study participants

Characteristics of study participants ($N = 2367$)	
Gender, *n* (%)	
Female	1369 (57.84)
Male	998 (42.16)
Age at interview, years, mean (s.d.)	47.5 (13.9)
Response to lithium, *n* (%)	
Favourable	660 (27.88)
Unfavourable	1707 (72.12)
Total Alda score, mean (s.d.)	4.12 (3.15)
Type of bipolar diagnosis, *n* (%)	
Bipolar type I	1890 (79.85)
Bipolar type II	440 (18.59)
Bipolar type III	7 (0.30)
Bipolar not specified	7 (0.30)
Schizoaffective bipolar disorder	18 (0.76)

Alda score, Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder.

details). The top ten contributing PGSs for the final mt-PGS model were scores for lithium responsiveness, bipolar disorder, major depression, COVID-19 susceptibility, heart failure, agreeableness, asthma, obsessive–compulsive disorder (OCD), extraversion and suicide attempt (see Fig. 2).

Cluster-level analysis showed that the psychiatric and behavioural (14 phenotypes), neurocognitive (5), autoimmune/inflammatory (3) and cardiometabolic (2) clusters explained 3.67, 0.72, 0.71 and 0.58% of the variability in lithium responsiveness, respectively. The renal function cluster contributed the least to the overall model, with the PGS for serum sodium level accounting for only ~0.01% of the variance in lithium responsiveness. A detailed breakdown of variance, explained by cluster-wise model and the final mt-PGS model, is provided in Table 2.

Multi-trait polygenic model for lithium response (categorical outcome)

Of the 60 PGSs initially considered, 21 were retained in the final mt-PGS model, collectively explaining 9.11% of the variance in lithium responsiveness on the liability scale (McFadden pseudo-R^2, s.e. = 0.017), and resulted in a prediction accuracy of 68.24% (95% CI: 64.98–71.66, Brier score 0.257) for lithium responders. The top contributing features in order of importance were as follows: the PGS for lithium responsiveness was the most dominant feature contributor to the final mt-PGS model parameters for the categorical outcome, followed by agreeableness, panic anxiety, chronic pain, OCD, Tourette syndrome, COVID-19 susceptibility, bipolar disorder, treatment-resistant schizophrenia and serum C-reactive protein (CRP) level (see Fig. 3).

Cluster-level analyses showed that PGSs from the psychiatric and behavioural, autoimmune/inflammatory, neurocognitive and cardiometabolic clusters explained, respectively, 6.52, 1.88, 1.64 and 0.68% of the variance in lithium responsiveness in liability scale, with corresponding AUCs of 62.98% (95% CI: 58.26–66.07, Brier score 0.264), 55.37% (95% CI: 51.62–59.30, Brier score 0.28), 51.99% (95% CI: 48.43–55.98, Brier score 0.279) and 52.43% (95% CI: 48.79–56.21, Brier score 0.298). No phenotype in the renal function cluster contributed meaningfully to lithium responsiveness (categorical outcome). The bootstrap bias-corrected calibration curves for all categorical models are provided in Supplementary

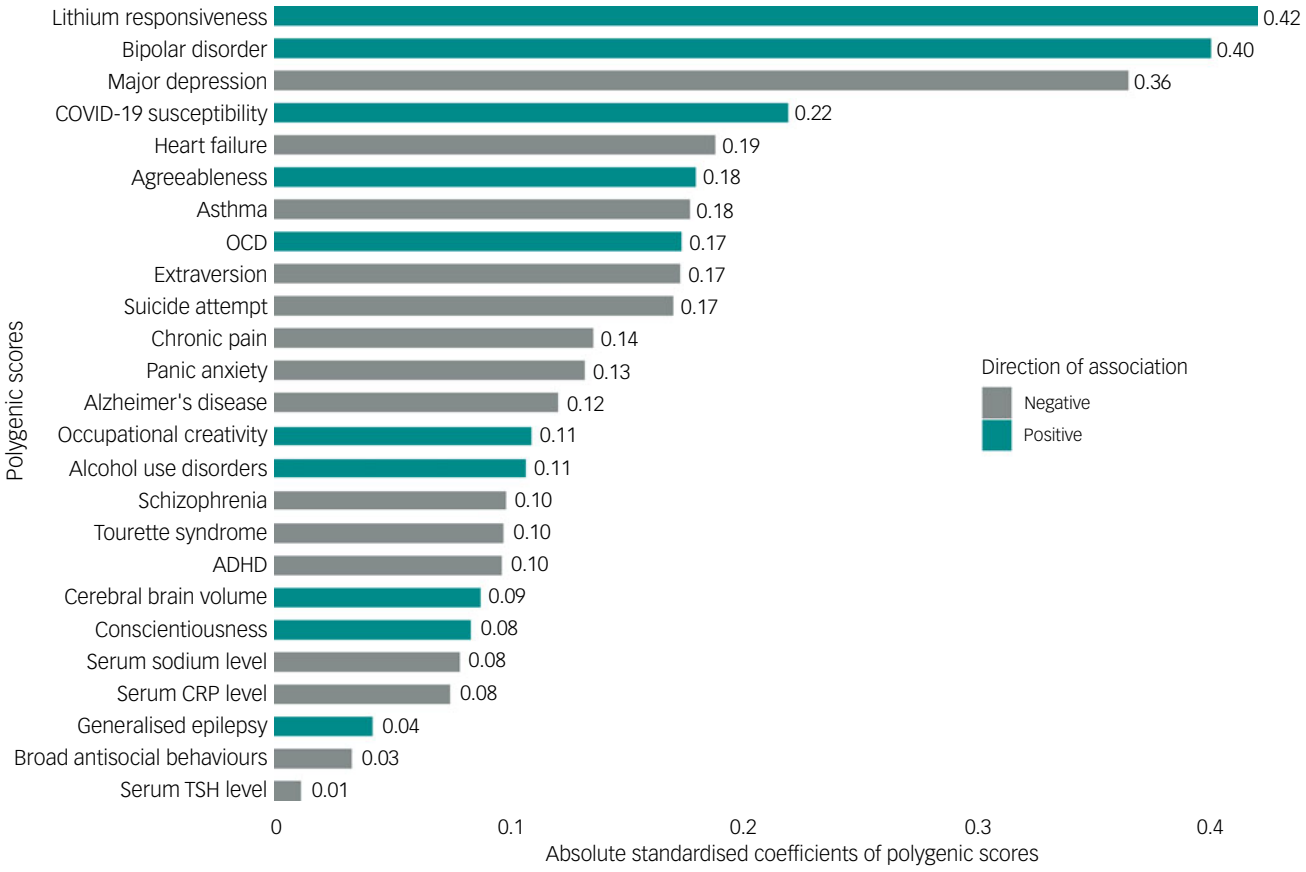


Fig. 2 Retained polygenic scores in the final mt-PGS model of continuous outcome. mt-PGS, multi-trait polygenic score; OCD, obsessive–compulsive disorder; ADHD, attention-deficit hyperactivity disorder; CRP, C-reactive protein; TSH, thyroid-stimulating hormone.

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Table 2 Continuous outcome model parameters in cluster-level and combined cluster models

Model	Contributing features	Model parameters		
		RMSE	MAE	R^2 (%)
Psychiatry and behavioural	Lithium responsiveness, bipolar disorder, MDD, SCZ, agreeableness, extraversion, conscientiousness, ADHD, panic anxiety, alcohol use disorders, OCD, broad antisocial behaviours, Tourette syndrome and suicidal attempt	3.26	2.84	3.67
Neurocognitive	Chronic pain, occupational creativity, Alzheimer's disease, cerebral brain volume and generalised epilepsy	3.32	2.92	0.72
Autoimmune/inflammatory	Asthma, COVID-19 susceptibility and serum CRP level	3.30	2.89	0.71
Cardiometabolic	Heart failure and serum TSH level	3.31	2.91	0.58
Renal function	Serum sodium level	3.33	2.92	~0.01
Final mt-PGS model	All the above	3.24	2.82	5.70

RMSE, root mean squared error; MAE, mean absolute error; R^2, explained variance; MDD, major depressive disorder; SCZ, schizophrenia; ADHD, attention-deficit hyperactivity disorder; OCD, obsessive–compulsive disorder; COVID-19, coronavirus 19; CRP, C-reactive protein; TSH, thyroid-stimulating hormone; mt-PGS, multi-trait polygenic score.

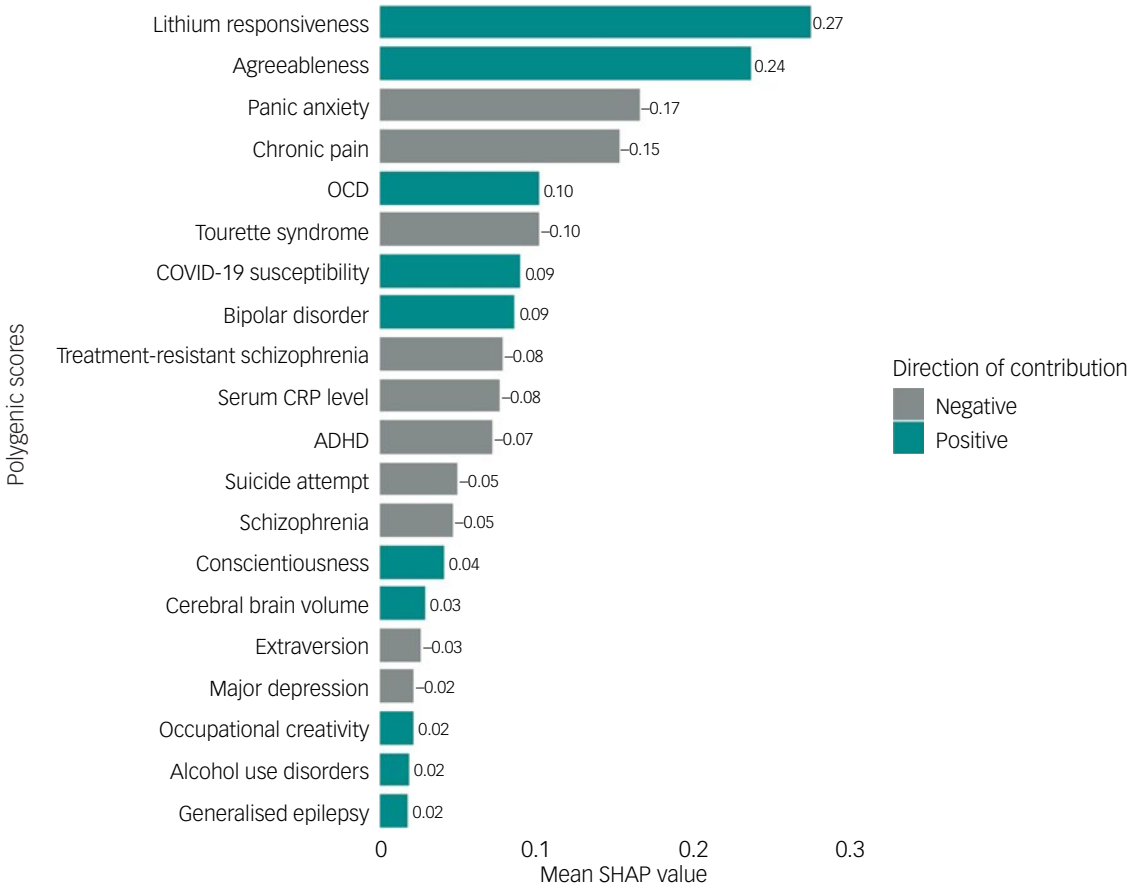


Fig. 3 The top 20 polygenic scores contributing to the final mt-PGS model of categorical outcome, ranked by importance from most to least (top to bottom). mt-PGS, multi-trait polygenic score; CRP, C-reactive protein; ADHD, attention-deficit hyperactivity disorder; SHAP, Shapley additive explanation; OCD, obsessive–compulsive disorder.

Fig. 4. A full summary of the categorical outcome model parameters in cluster-wise and final mt-PGS models is provided in Supplementary Table 6.

Discussion

This study demonstrates that a mt-PGS approach, integrating genetic risk information across a broad range of phenotypes implicated in lithium pharmacology and/or the aetiology of bipolar disorder, substantially improves the prediction of lithium treatment response. The mt-PGS explained 5.70 and 9.11% of variance in the continuous and categorical lithium treatment outcomes, respectively, achieving an AUC of 68.24% (95% CI: 64.98–71.66). These results represent a substantial improvement over previously reported single-trait PGSs, such as those based on SCZ,[13] MDD,[14] both SCZ and MDD,[21] ADHD[15] or lithium responsiveness itself,[17] which typically explained only 1.0–2.6% of the variance in lithium responsiveness. However, the model predictive performance remained lower than that observed in previous work combining meta-analysed PGSs for MDD and SCZ with clinical data,[46] underscoring the value of integrating mt-PGS with clinical

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phenotypic features to further improve prediction and support potential clinical translation. The superior performance of the mt-PGS model over single-trait PGSs is probably due to several factors. First, by leveraging polygenic information from multiple, genetically correlated phenotypes, the model captures a broader and more relevant spectrum of genetic variance.[28] This approach aligns with recent research showing that multi-trait models, especially those integrating traits with shared biological pathways, consistently outperform single-trait models in complex trait prediction.[21,47] Second, the inclusion of PGSs from medical and behavioural phenotypes that are already known to be associated with psychiatric conditions, as well as pharmacogenomic phenotypes, increases statistical power and biological specificity.[48]

Polygenic scores for phenotypes within the psychiatric and behavioural cluster emerged as the most strongly associated features in predicting lithium responsiveness, with R^2 of 3.67% in the continuous outcome model and McFadden pseudo-R^2 of 6.52% in the categorical outcome model. This strong association is expected, given that the psychiatric and behavioural phenotype shares a similar genetic architecture with both bipolar disorder and lithium responsiveness, as established in previous genetic studies.[28] Of the individual phenotypes, the top predictors were the PGSs for bipolar disorder and the lithium responsiveness phenotype, both of which positively associated with clinical lithium response, echoing earlier research[17] and supporting the idea that individuals with a higher genetic predisposition for bipolar disorder and lithium response are more likely to benefit from lithium treatment. Conversely, PGSs for MDD, SCZ, ADHD, panic anxiety and broad antisocial behaviour were negatively associated with lithium responsiveness. These findings may appear counterintuitive, given the substantial genetic correlation between bipolar disorder and MDD or SCZ ($rg \sim 0.7$).[49] However, a positive correlation does not mean that all MDD/SCZ-related genetic variation increases bipolar disorder liability or influences lithium response in the same level of effect and/or consistent direction. Instead, there are shared and unique components, some of which may relate differently to treatment response. This is in line with clinical observations[13–15,21] showing that there might be a unique biological signature of bipolar disorder directly linked to better lithium response but not shared with MDD or SCZ. Statistically, our mt-PGS model can simultaneously adjust for bipolar disorder, SCZ and MDD PGSs and separate their overlapping and non-overlapping genetic components, reducing the counterintuitive effects.

Consistent with previous findings in psychiatric pharmacotherapy,[50] positive associations were observed between agreeableness and conscientiousness personality traits and lithium treatment response. These associations may be mediated through underlying genetic mechanisms[51] and/or through the influence of these traits on medication adherence and therapeutic engagement, and supportive behaviours.[50] The findings were further supported by genetic evidence showing that the PGSs for openness and conscientiousness have previously been associated with favourable antidepressant treatment outcomes, such as response and remission.[52] Collectively, these converging lines of evidence suggest that personality traits may represent broadly generalisable modifiers of psychotropic treatment response across diagnostic categories, potentially via shared genetic mechanisms and/or observable behavioural, cognitive and affective mechanisms that influence treatment adherence, symptom perception, stress reactivity and clinician–patient interaction.[53]

Autoimmune and inflammatory PGSs explained a modest but notable proportion of lithium responsiveness, accounting for 0.71–1.64% of the variance. Within this group, PGSs for asthma and serum CRP levels were negatively associated with lithium response, indicating that individuals with higher genetic risk for these inflammatory conditions are less likely to benefit from lithium treatment. This finding aligns with the established role of inflammation in bipolar disorder, where elevated CRP and chronic low-grade inflammation are linked to greater symptom severity and shorter duration of effective lithium therapy. Lithium's recognised immune-modulating properties, including its influence on proinflammatory cytokine regulation,[54] may underlie some of its therapeutic effects in mood disorders. The negative association between serum CRP PGS and lithium response supports the hypothesis that lithium's anti-inflammatory action could be a key mechanism in its efficacy, and that individuals with a genetic predisposition to greater inflammation may experience less benefit.[55] Furthermore, immune-related gene sets have been shown to be overrepresented in lithium resistance, with activation of inflammatory and adaptive immune pathways observed in non-responders.[31]

Interestingly, the study found a significant positive association between the PGS for COVID-19 susceptibility and lithium response. This is perhaps surprising, but lithium has demonstrated antiviral properties including activity against COVID-19, in preclinical studies.[56] In addition, epidemiological evidence indicates that individuals treated with lithium have a decreased risk of respiratory infections,[57] supporting broader immunoprotective or anti-inflammatory effects. One possible explanation is that genetic variants conferring susceptibility to COVID-19 may overlap with immune pathways that also enhance lithium's therapeutic effects, or that individuals with these variants may have an immune profile that is particularly responsive to lithium's modulatory actions. However, this association warrants further investigation to clarify the underlying biological mechanisms.

We observed a negative association between PGSs for heart failure, serum TSH levels and Alzheimer's disease with lithium responsiveness. This suggests that individuals with a higher genetic predisposition to these phenotypes are less likely to respond favourably to lithium treatment. Although these results seem to be in conflict with lithium's established neuroprotective[58] and cardioprotective actions,[59] it might be because these conditions are characterised by advanced pathological changes, including chronic inflammation, oxidative stress, mitochondrial impairment, neuronal loss and disrupted neurovascular coupling, that counteract lithium's protective mechanisms.[60] Cardiometabolic diseases such as heart failure have been associated with an increased risk of renal impairment, which can reduce lithium clearance leading to lithium accumulation and toxicity, thereby altering its therapeutic efficacy.[61] Hypothyroidism is a well-documented side-effect of long-term lithium therapy, and a high genetic loading for this condition may reduce the therapeutic benefits of lithium.[62] From a clinical perspective, our results should therefore be viewed as risk-stratification signals rather than treatment-exclusion criteria. They highlight the importance of considering broader biological vulnerability, including neurodegenerative and cardiometabolic burden, when evaluating expected lithium response, while reinforcing the fact that lithium remains an appropriate and potentially protective treatment for many patients. Additional factors, such as treatment adherence, medical comorbidity and illness chronicity, may further contribute to these associations and warrant investigation in larger, longitudinal studies.

Chronic pain emerged as a top contributor and showed a negative association with lithium treatment response. This may reflect lithium's interactions with pain-modulation pathways; lithium has been shown to inhibit neuromodulators such as substance P and vasoactive intestinal peptide, which are implicated in the perception of pain.[63] Elevated substance P levels have been reported in MDD and chronic pain, providing a plausible biological

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context for the poorer lithium response observed in patients with comorbid MDD and chronic pain, a subgroup characterised by high rates of treatment resistance.[64] In addition, the observed strong genetic correlation between chronic pain and MDD may further influence lithium treatment response.

Limitations

Our study should be interpreted in light of important limitations. First, although the ConLi+Gen cohort represents the largest available data-set for studying lithium treatment outcomes in bipolar disorder, its sample size remains modest compared with cohorts used in other large-scale genetic studies. This limitation may reduce the statistical power to generate highly precise PGSs and could affect the stability of our findings.[9,19,20] Second, the application of machine learning analyses to a relatively small sample raises the possibility of overfitting, which can artificially inflate prediction accuracy.[35] Although we employed nested cross-validation and careful hyperparameter tuning to mitigate this risk, the potential for overestimation of predictive performance cannot be entirely excluded. Third, although our model explains a greater proportion of the variance in lithium responsiveness than that reported in previous studies, its overall accuracy and calibration are poor, indicating important limitations for direct clinical translation. Fourth, our analysis was restricted to individuals of European ancestry, which means the findings may not be generalisable to populations with different genetic backgrounds and could limit the broader applicability of our results. Fifth, our PGSs were constructed using GWAS summary statistics, which primarily capture common genetic variants and may miss the influence of rare variants that could also affect lithium response. Sixth, the PGS for lithium responsiveness was calculated using the ConLi+Gen cohort as both the discovery and target data-set, employing a leave-one-country-out procedure. This approach may overestimate the effect of the lithium responsiveness phenotype and therefore requires validation analysis using an independent target cohort. Seventh, the predictive performance of each PGS depends on the sample size of the target cohort (discovery GWAS) and trait heritability, which may have influenced the selection of PGSs retained in our models. Finally, the set of polygenic predictors/phenotypes selected within each cluster may not be exhaustive or fully representative of all features potentially associated with lithium responsiveness, because additional relevant predictors may yet be identified as the field advances. These limitations highlight the need for larger, more diverse cohorts, prospective study designs and the inclusion of rare variant analyses in future research to further refine and validate predictive models for lithium response in bipolar disorder.

Implications

In summary, our study highlights that the predictive power of PGSs for lithium responsiveness can be substantially increased by integrating genetic variants from multiple pharmacogenomic and disease-associated traits, rather than relying solely on single-phenotype scores. This multi-trait approach takes advantage of the shared genetic architecture among related phenotypes, thereby capturing a wider and more clinically relevant spectrum of genetic risk factors. The integration of genomics with clinical data has already demonstrated considerable promise; for example, Cearns et al showed that combining PGSs for MDD and SCZ with clinical variables using machine learning algorithms explained nearly 14% of the variance in lithium responsiveness, outperforming models based on either genetic or clinical data alone.[46] Building on this, further improvements in predictive accuracy are probably achievable by adopting mt-PGS approaches in combination with detailed clinical profiles. Looking ahead, future research should prioritise integrating pharmacomulti-omics data – including genomics, metabolomics, neuroimaging and clinical variables – with the goal of developing even more robust and personalised predictive models. Such integrative and data-driven strategies hold great promise for advancing precision psychiatry, ultimately enabling more tailored and effective treatment selection for individuals with bipolar disorder and other complex psychiatric conditions.

The preprint version of this work is available elsewhere.[65]

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Supplementary material

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Data availability

All data used in this analysis are available to ConLi+Gen members. See http://www.conligen.org/ for further information.

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Author contributions

A.T.A. conceived and designed the project and secured a fellowship to lead the study. N.T.S. developed the research proposal, conducted the statistical analysis, interpreted the findings and drafted the manuscript. A.T.A., S.R.C., O.S. and S.H. provided supervision and critically reviewed the data analysis steps and manuscript draft. All authors contributed genetic and clinical data, provided feedback and made significant intellectual contributions to the manuscript.

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Software and code-sharing

The software used included polygenic risk score–continuous shrinkage (PRS-CS version 1.1.0 for Linux; Tian Ge et al, Massachusetts General Hospital, Boston,Massachusetts, USA; https://github.com/getian107/PRScs) and PLINK version 2.0 for Linux (Purcell S and Chang C; https://www.cog-genomics.org/plink/2.0/). The custom codes used in this study will be made available upon reasonable request to the corresponding author.

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