*Research Article*

*Association of ADHD and depression polygenic scores with lithium response: A Consortium for Lithium Genetics study*

Brandon J Coombes [1], Vincent Millischer [2,3], Anthony Batzler [1], Beth Larrabee [1], Liping Hou [4], Sergi Papiol [5,6], Urs Heilbronner [5], Mazda Adli [7], Kazufumi Akiyama [8], Nirmala Akula [4], Azmeraw T Amare [9,10], Raffaella Ardau [11], Barbara Arias [12], Jean-Michel Aubry [13], Lena Backlund [14,15], Michael Bauer [16], Bernhard T Baune [17,18,19], Frank Bellivier [20], Antoni Benabarre [21], Susanne Bengesser [22], Abesh Kumar Bhattacharjee [23], Pablo Cervantes [24], Hsi-Chung Chen [25], Caterina Chillotti [11], Sven Cichon [26,27,28], Scott R Clark [9], Francesc Colom [29,30], Cristiana Cruceanu [31], Piotr M Czerski [32], Nina Dalkner [22], Franziska Degenhardt [33], Maria Del Zompo [34], J Raymond DePaulo [35], Bruno Étain [20], Peter Falkai [6], Ewa Ferensztajn-Rochowiak [36], Andreas J Forstner [27,33,37], Louise Frisen [14,15], Sébastien Gard [38], Julie S Garnham [39], Fernando S Goes [35], Maria Grigoroiu-Serbanescu [40], Paul Grof [41], Ryota Hashimoto [42,43], Joanna Hauser [32], Stefan Herms [28,33], Per Hoffmann [28,33], Stephane Jamain [6], Esther Jiménez [21], Jean-Pierre Kahn [44], Layla Kassem [4], Tadafumi Kato [45], John R Kelsoe [23], Sarah Kittel-Schneider [46], Barbara König [47], Po-Hsiu Kuo [48], Ichiro Kusumi [49], Gonzalo Laje [4], Mikael Landén [50,51], Catharina Lavebratt [14,15], Marion Leboyer [52,53,54], Susan G Leckband [55], Mario Maj [56], Mirko Manchia [57,58], Lina Martinsson [59], Michael J McCarthy [23,60], Susan L McElroy [61], Philip B Mitchell [62], Marina Mitjans [63], Francis M Mondimore [35], Palmiero Monteleone [56,64], Caroline M Nievergelt [23], Markus M Nöthen [33], Tomas Novák [65], Claire O'Donovan [39], Urban Osby [66], Norio Ozaki [67], Andrea Pfennig [16], Claudia Pisanu [34], James B Potash [35], Andreas Reif [46], Eva Reininghaus [22], Marcella Rietschel [68], Guy A Rouleau [69], Janusz K Rybakowski [36], Martin Schalling [14,15], Peter R Schofield [70,71], Klaus Oliver Schubert [9,72], Barbara W Schweizer [35], Giovanni Severino [34], Tatyana Shekhtman [23], Paul D Shilling [23], Katzutaka Shimoda [73], Christian Simhandl [74], Claire M Slaney [39], Alessio Squassina [34], Thomas Stamm [7], Pavla Stopkova [65], Alfonso Tortorella [75], Gustavo Turecki [31], Eduard Vieta [21], Stephanie H Witt [68], Peter P Zandi [76], Janice M Fullerton [70,71], Martin Alda [39], Mark A Frye [77], Thomas G Schulze [4,5,35,68,78], Francis J McMahon [4], Joanna M Biernacka [1,77]

1 Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN, USA.

2 Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria

3 Department for Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden.

4 Intramural Research Program, National Institute of Mental Health, National Institutes of Health, US Department of Health & Human Services, Bethesda, MD, USA.

5 Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Nußbaumstr. 7, 80336 Munich, Germany.

6 Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University Munich, Munich, Germany.

7 Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Campus Charité Mitte, Berlin, Germany.

8 Department of Biological Psychiatry and Neuroscience, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan.

9 Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA, Australia.

10 South Australian Academic Health Science and Translation Centre, South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA, Australia.

11 Unit of Clinical Pharmacology, Hospital University Agency of Cagliari, Cagliari, Italy.

12 Unitat de Zoologia i Antropologia Biològica (Dpt. Biologia Evolutiva, Ecologia i Ciències Ambientals), Facultat de Biologia and Institut de Biomedicina (IBUB), University of Barcelona, CIBERSAM, Barcelona, Spain.

13 Department of Psychiatry, Mood Disorders Unit, HUG - Geneva University Hospitals, Geneva, Switzerland.

14 Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden.

15 Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden.

16 Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Medical Faculty, Technische Universität Dresden, Dresden, Germany.

17 Department of Psychiatry, University of Münster, Münster, Germany. Department of Psychiatry, University of Münster, Münster, Germany.

18 Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, Australia.

19 The Florey Institute of Neuroscience and Mental Health, The University of Melbourne Parkville, VIC, Australia.

20 INSERM UMR-S 1144, Université Paris Diderot, Département de Psychiatrie et de Médecine Addictologique, AP-HP, Groupe Hospitalier Saint-Louis-Lariboisière-F.Widal, Paris, France.

21 Bipolar Disorder Program, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain.

22 Department of Psychiatry and Psychotherapeutic Medicine, Research Unit for bipolar affective disorder, Medical University of Graz, Graz, Austria.

23 Department of Psychiatry, University of California San Diego, La Jolla, CA, USA.

24 The Neuromodulation Unit, McGill University Health Centre, Montreal, QC, Canada. The Neuromodulation Unit, McGill University Health Centre, Montreal, QC, Canada.

25 Department of Psychiatry & Center of Sleep Disorders, National Taiwan University Hospital, Taipei, Taiwan.

26 Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland.

27 Institute of Neuroscience and Medicine (INM-1), Research Center Jülich, Jülich, Germany.

28 Human Genomics Research Group, Department of Biomedicine, University Hospital Basel, Basel, Switzerland.

29 Mental Health Research Group, IMIM-Hospital del Mar, Barcelona, Catalonia, Spain.

30 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain.

31 Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada.

32 Psychiatric Genetic Unit, Poznan University of Medical Sciences, Poznan, Poland.

33 Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany.

34 Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy.

35 Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA.

36 Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland.

37 Centre for Human Genetics, University of Marburg, Marburg, Germany.

38 Service de psychiatrie, Hôpital Charles Perrens, Bordeaux, France.

39 Department of Psychiatry, Dalhousie University, Halifax, NS, Canada.

40 Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania.

41 Mood Disorders Center of Ottawa, Ottawa, ON, Canada.

42 Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan.

43 Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, Japan.

44 Service de Psychiatrie et Psychologie Clinique, Centre Psychothérapique de Nancy - Université de Lorraine, Nancy, France.

45 Department of Psychiatry and Behavioral Science, Juntendo University Graduate School of Medicine, Tokyo, Japan.

46 Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt, Germany.

47 Department of Psychiatry and Psychotherapeutic Medicine, Landesklinikum Neunkirchen, Neunkirchen, Austria.

48 Department of Public Health & Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan.

49 Department of Psychiatry, Hokkaido University Graduate School of Medicine, Sapporo, Japan.

50 Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the Gothenburg University, Gothenburg, Sweden.

51 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

52 AP-HP, Hôpital Henri Mondor, Département Médico-Universitaire de Psychiatrie et d’Addictologie (DMU IMPACT), Fédération Hospitalo-Universitaire de Médecine de Précision (FHU ADAPT) F-94010, France.

53 Université Paris Est Créteil, INSERM U955, IMRB, Laboratoire Neuro-Psychiatrie translationnelle, F-94010 Créteil, France.

54 Fondation FondaMental.

55 Office of Mental Health, VA San Diego Healthcare System, San Diego, CA, USA.

56 Department of Psychiatry, University of Campania ‘Luigi Vanvitelli’, Naples, Italy.

57 Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy.

58 Department of Pharmacology, Dalhousie University, Halifax, NS, Canada.

59 Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden.

60 Department of Psychiatry, VA San Diego Healthcare System, San Diego, CA, USA.

61 Department of Psychiatry, Lindner Center of Hope / University of Cincinnati, Mason, OH, USA.

62 School of Psychiatry, University of New South Wales, Sydney, NSW, Australia.

63 Departament de Genètica, Microbiologia i Estadística, Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain; Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Spain; Centro de Investigación Biomédica en Salud Mental (CIBERSAM), Madrid, Spain.

64 Neurosciences Section, Department of Medicine, Surgery and Dentistry ‘Scuola Medica Salernitana’, University of Salerno, Salerno, Italy.

65 National Institute of Mental Health, Klecany, Czech Republic.

66 Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet and Center for Molecular Medicine, Karolinska University Hospital, Stockholm, Sweden.

67 Department of Psychiatry & Department of Child and Adolescent Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan.

68 Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany.

69 Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada.

70 Neuroscience Research Australia, Sydney, NSW, Australia.

71 School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia.

72 Northern Adelaide Local Health Network, Mental Health Services, Adelaide, SA, Australia.

73 Department of Psychiatry, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan.

74 Bipolar Center Wiener Neustadt, Sigmund Freud University, Medical Faculty, Vienna, Austria.

75 Department of Psychiatry, University of Perugia, Perugia, Italy.

76 Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.

77 Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA.

78 Department of Psychiatry and Psychotherapy, University Medical Center (UMG), Georg-August University Göttingen, Göttingen, Germany.

Short title: Association of ADHD and MDD PRS with lithium response in ConLiGen

Corresponding Author:

Brandon J. Coombes

Department of Quantitative Health Sciences

Mayo Clinic

200 First St. SW

Rochester, MN 55905

Tel: (507) 293-0051

E-mail: coombes.brandon@mayo.edu

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# Abstract

Response to lithium varies widely between individuals with bipolar disorder (BD). Polygenic risk scores (PRS) can uncover pharmacogenomics effects and may help predict drug response. Patients (N=2510) with BD were assessed for long-term lithium response in the Consortium on Lithium Genetics (ConLiGen) using the Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder score. PRS for attention deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), and schizophrenia were computed using *lassosum* and in a model including all three PRS and other covariates, the PRS of ADHD (β = -0.14; 95% CI -0.24 to -0.03; p-value = 0.010) and MDD (β = -0.16; 95% CI -0.27 to -0.04; p-value = 0.005) predicted worse quantitative lithium response. Higher schizophrenia PRS was associated with higher rates of medication non-adherence (OR = 1.61; 95% CI 1.34 to 1.93; p-value = 2e-7). This study indicates that genetic risk for ADHD and depression may influence lithium treatment response. Interestingly, higher SCZ PRS was associated with poor adherence, which can negatively impact treatment response. Incorporating genetic risk of ADHD, depression, and schizophrenia in combination with clinical risk may lead to better clinical care for patients with BD.

# Introduction

Bipolar disorder (BD) is a severe psychiatric disorder characterized by episodes of mania and depressive mood states. The main BD subtypes, type I and II, each have an estimated lifetime prevalence of approximately 1%[(1,2)](https://paperpile.com/c/J9xJYr/kCrs%2BQYfW). As a lifelong and recurrent illness, BD is associated with a high level of comorbidity and reduced quality of life, and often results in recurrent suicidality.

Lithium, anti-epileptic drug mood stabilizers (e.g. valproate/divalproex and lamotrigine), antipsychotics, and antidepressants are commonly prescribed treatments for BD. However, treatment response varies widely between individuals, and many patients cycle through different medications before they find an effective treatment with minimal side effects. Lithium is currently regarded as the first-line treatment due to its effectiveness in preventing both manic and depressive episodes[(3)](https://paperpile.com/c/J9xJYr/7zHU), suicide[(4)](https://paperpile.com/c/J9xJYr/ILGV), and hospitalization[(5)](https://paperpile.com/c/J9xJYr/3Kjh). However, only about 30% of patients show full response to the drug[(4,6)](https://paperpile.com/c/J9xJYr/5LzO%2BILGV) and, currently there are few clinical predictors such as episodic course, later age-of-onset and absence of rapid cycling that may predict lithium response[(7,8)](https://paperpile.com/c/J9xJYr/sXHE%2BJeGD).

Pharmacogenomic studies use genetics to better understand the biological mechanisms of treatment response and aim to develop biomarkers for response. Recent genome-wide association studies (GWAS) have shown that genetic variation could play an important role in mood-stabilization in response to pharmacotherapy for BD[(6,9–12)](https://paperpile.com/c/J9xJYr/5LzO%2B8lEP%2BR5hy%2BnB8d%2BxeyN). The largest of these GWAS was performed by the International Consortium on Lithium Genetics (ConLiGen)[(6)](https://paperpile.com/c/J9xJYr/5LzO) and included over 2500 patients that have been treated with lithium. By creating polygenic risk scores (PRS) in this sample, it was recently shown that higher genetic loading for schizophrenia (SCZ) and major depressive disorder (MDD) is associated with poorer response to lithium[(13,14)](https://paperpile.com/c/J9xJYr/ZRIx%2BuZGb). Thus, while pharmacogenomic GWAS sample sizes still remain too small to have power to robustly detect individual variants associated with treatment response, PRS derived from large, well-powered GWAS of psychiatric disorders and other traits have begun to provide insight into the genetic factors that contribute to treatment response.

MDD and SCZ PRS were important early study targets, BD being closely related with these two disorders and lithium response being associated with some clinical features specific to them (e.g. psychotic symptoms)[(13,14)](https://paperpile.com/c/J9xJYr/ZRIx%2BuZGb),[(15)](https://paperpile.com/c/J9xJYr/HHZF). However, the symptomatic, syndromicand genetic overlap in BD and attention-deficit/hyperactivity disorder (ADHD)[(16–18)](https://paperpile.com/c/J9xJYr/tzpf%2B7rGw%2BAgtK) and the association of a history of ADHD with reduced lithium response[(19)](https://paperpile.com/c/J9xJYr/MXui), motivate the targeted investigation of ADHD PRS as a potential predictor of lithium treatment response.

Here, we aim to use PRS analyses to assess whether higher genetic loading for ADHD is associated with improved or poorer response to lithium. Additionally, we incorporate the joint effect of the ADHD PRS with the previously identified PRS already shown to be associated with lithium response (SCZ and MDD). Finally, we explore how these PRS are associated with confounders of treatment response measurements.

# Materials and Methods

## Studies

Ascertainment and diagnostic assessment for the ConLiGen study has been described previously[(6,20)](https://paperpile.com/c/J9xJYr/vHe2%2B5LzO). Briefly, data on gender, lithium response, and genotypes for patients with a DSM-III or DSM-IV diagnosis of BD were collected in two waves from 23 sites in 15 countries. The dataset, which contained individuals of European (EUR) and East Asian (EAS) ancestry (Japan and Taiwan), was grouped by wave and ancestry: EUR1, EUR2, JPT1, and TAI2. Phenotyping, genotyping, QC and imputation are fully described below and the sample sizes for all studies through quality control (QC) steps in the analysis are shown in Supplementary Table 1.

## Treatment Response Measures

The Alda scale was used to evaluate long-term treatment response to lithium for all participants. This scale is a retrospective assessment and is the most widely used clinical measure of lithium response phenotypes[(21)](https://paperpile.com/c/J9xJYr/InH5). The Alda scale quantifies symptom improvement in the course of treatment (A score, range 0–10) and five criteria (B score) to assess possible confounding factors, each scored 0, 1, or 2 (more description in Statistical Analyses section). Alda scores showed a moderate to substantial inter-rater reliability in this sample[(21,22)](https://paperpile.com/c/J9xJYr/InH5%2BlGxO). Patients with incomplete information on B score (N = 37) were removed from the analysis. Patients were considered lithium responders if they had a total Alda score (A score - B score) of 7 or greater, consistent with prior studies[(6,22)](https://paperpile.com/c/J9xJYr/5LzO%2BlGxO).

## Genotyping, Quality Control, and Imputation

Genotyping was performed in eleven different batches. For each genotyping batch, a standard QC pipeline was used to remove SNPs with low call-rate (< 95%) or showing departure from Hardy-Weinberg Equilibrium (HWE; p < 1x10-6) and to remove subjects with low call-rate (< 95%), outlier heterozygosity, or mismatched sex. A total of 2587 participants with phenotype data were genotyped and 2554 remained after the first QC step. After QC of each batch, the batches were combined to check for relatedness (kinship coefficient[(23)](https://paperpile.com/c/J9xJYr/eRXb) threshold = 0.2) in the entire study. From each related pair (N = 4), we removed the subject with the highest B score (i.e. lowest confidence in A score) leaving 2550 samples to be imputed. Further details can be found in Supplementary Table 1.

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Each genotyping batch was imputed using the Human Reference Consortium (HRC)[(24)](https://paperpile.com/c/J9xJYr/Ig38) reference population on the Michigan Impute Server (MIS)[(25)](https://paperpile.com/c/J9xJYr/YvHP). The Wrayner pre-imputation tool was used to remove SNPs with allele frequency differences compared to the HRC greater than 0.2 using all samples (including Asian ancestry). A total of 5,896,308 well-imputed variants across all batches (dosage R2 > 0.7 and MAF > 0.01) were used for the subsequent analyses. Because of updated QC and imputation (see Supplementary Table 1), the resulting dataset differs from that reported in Hou *et al*.[(6)](https://paperpile.com/c/J9xJYr/5LzO) with fewer samples and more SNPs used in the current analyses.

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## Polygenic Risk Scores (PRS)

PRS for ADHD[(26)](https://paperpile.com/c/J9xJYr/XpKc), MDD[(27)](https://paperpile.com/c/J9xJYr/4PvY), and SCZ[(28)](https://paperpile.com/c/J9xJYr/p0E8) were constructed using *lassosum* [(29)](https://paperpile.com/c/J9xJYr/KQpc), a penalized regression approach which uses a lasso-penalty term (λ) to perform a “pruning-like” procedure for variants in linkage disequilibrium, and a thresholding parameter (s) that ranges from soft-thresholding (s=0), similar to p-value thresholding, to hard thresholding. We used a grid of values for the two parameters: {λ = 0.001, 0.003, and 0.01} and {s = 0.2, 0.5, 0.9, and 1} as recommended[(29)](https://paperpile.com/c/J9xJYr/KQpc). Within each cohort (EUR1, EUR2, JPT, TAI), each PRS was then standardized to have mean equal to zero and standard deviation (SD) equal to one. Finally, within each cohort, we performed a principal component analysis (PCA) on each set of PRS across different parameter settings (grid of λ and s) and kept the first PC. This PRS-PCA approach avoids optimizing a given PRS to the outcome and thus avoids correcting for the resulting inflated type-I error[(30)](https://paperpile.com/c/J9xJYr/ExrO).

## Statistical Analyses

As a primary analysis, we assessed the association of treatment response with PRS using two different outcomes: 1) responder/non-responder or 2) Alda A score. The binary response was modeled using logistic regression. For the quantitative response, we used a generalized least squares (GLS) model (using the *nlme* R package) to adjust for B score and to estimate study-specific error variances, because the variance of A score differed between the studies (Supplementary Fig. 1). Within each cohort, we first regressed the ADHD PRS as well as the known associated PRS (MDD and SCZ) one at a time in our models. For EUR1 and EUR2 cohorts, the models were also adjusted for the first four genomic PCs to account for variation in European ancestries. We then used a fixed-effect meta-analysis to combine the PRS results across cohorts. We estimated the average variance explained by each PRS using R2 (Nagelkerke’s pseudo-R2 for binary outcomes using the *rsq* R package) within each cohort and using a weighted average R2 for each meta-analysis. Next, to assess the joint effect of ADHD with the other two PRS (MDD and SCZ), we included all three PRS in a multivariate model to test the association of each trait’s PRS with lithium response after adjusting for the other trait PRS. We examined the heterogeneity of the PRS associations among the sites. We used a Bonferroni correction to adjust the significance threshold in our primary analysis to control for testing the ADHD PRS with the two different outcomes in the analysis (p = 0.05/2 = 0.025). We do not adjust our significance threshold for multiple PRS because the SCZ and MDD PRS were already known to be individually associated with treatment response.

As a secondary analysis, we examined the PRS associations with the Alda B score as well as the individual components of the B score: number of episodes off treatment (4 or more episodes vs. less than 4), frequency of episodes off treatment (average to high vs. low or only one episode), length of use of lithium (2 or more years vs. less than 2 years), medication adherence (poor vs. good/excellent), and lithium monotherapy (lithium-only vs. lithium + sleep/antidepressant/antipsychotic medications). All statistical analyses were performed in R 3.5.2.

# Results

## Sample characteristics and lithium response

After QC and imputation, a total of 2510 patients were included in the analysis including 2299 of European ancestries (1057 from the EUR1 sample and 1242 from EUR2) and 211 of Asian ancestries (126 from JPT1 and 85 from TAI2). Of the 2510 patients in the study (mean [SD] age, 47.1 [13.9] years), 1434 were women and 1076 were men. Patients’ response to lithium varied widely (Supplementary Figure 1). The average Alda total score was 6.2 [3.0] with patients of European ancestries responding better on average than those of Asian ancestries (6.3 [2.9] vs. 5.3 [3.5], respectively; p-value = 0.0009). Furthermore, 688 patients (27.4%) were classified as responding well to lithium (Alda score ≥ 7) with patients of European ancestries having a better response rate than patients of Asian ancestries (28.1% vs. 19.9%, respectively; p-value = 0.01). Table 1 shows the distribution of each individual component in the Alda score.

After adjusting for site differences, four of the five individual components of the B score were associated with poorer treatment response. The A score of patients with an average to high frequency of episodes off lithium was on average 0.52 points less than those with low frequency (SE=0.14; p=0.0003). Patients taking lithium for over two years had an A score 1.24 points higher (SE=0.15; p<2e-16). Patients with poor adherence had an A score 1.29 points lower (SE=0.23; p < 0.0001). Finally, patients taking lithium-only had an A score 1.56 points higher (SE =0.13; p < 0.0001). The associations of these individual B score components with the A score remained significant in a multivariate model including all B components. This suggests that rather than including B score directly in a lithium response measure (e.g. Alda total score or dichotomized Alda total score), B score can be included as a covariate in the model to account for potential confounding.

## PRS association with treatment response

We estimated the association of the ADHD PRS and the two previously established PRS (MDD and SCZ) individually with treatment response (Fig. 1). Higher ADHD PRS was associated with poorer quantitative response (change in Alda A score per 1SD increase in PRS = -0.15; R2 = 0.18%; p-value = 0.004) and no association with lithium non-response (OR per 1SD increase in PRS = 0.92; R2 = 0.14%; p-value = 0.059). The ADHD PRS association with quantitative response was driven by the EUR sample (β = -0.16; R2 = 0.19%; p-value = 0.003) with no evidence of association in the EAS sample (β = -0.02; R2 = 0%; p-value = 0.95). As has been previously shown[(14)](https://paperpile.com/c/J9xJYr/uZGb), higher genetic loading for MDD was associated with lithium non-response (OR = 0.86; R2 = 0.76%; p-value = 0.002) and worse quantitative response (β = -0.15; R2 = 0.12%; p-value = 0.006) in the full sample. Unlike previous analyses in the ConLiGen sample[(13)](https://paperpile.com/c/J9xJYr/ZRIx), higher PRS for SCZ showed only weak evidence of association with lithium non-response (OR = 0.88; R2 = 0.57%; p-value = 0.013), and showed no effect on quantitative response (β = 0.04; R2 = 0.12%; p-value = 0.5). There was low heterogeneity of the ADHD or MDD PRS associations between sites with no site-specific outlier effects driving our findings (Supplementary Figs. 2 & 3).

We next estimated the association of each PRS with lithium treatment response in a multivariate model including all three PRS. Prior to fitting the multivariate model, we evaluated the correlations among the PRS. The PRS correlations were highest between MDD and SCZ (r = 0.30) and lowest between SCZ and ADHD (r = 0.05). After adjusting for the other PRS, the effects of ADHD (β = -0.14; p-value = 0.010) and MDD (β = -0.16; p-value = 0.005) remained significant predictors of worse quantitative response. MDD (OR = 0.89; p-value = 0.021) was the only PRS associated with lithium non-response after adjusting for the other PRS. The PRS for SCZ showed no evidence of association with treatment response after accounting for the genetic contributions of ADHD and MDD PRS.

## PRS association with B score

As a secondary analysis, we assessed each PRS’s association with the B score, a measure of uncertainty in treatment response ascertainment, and its components (Fig. 2). The B score is used in the calculation of the total Alda score (A-B) and thus is used in assignment to responder/non-responder groups. In the full sample, higher genetic load for SCZ was associated with a higher total B score (β = 0.120; p-value = 0.0002). This association was driven by higher SCZ PRS being associated with higher rates of medication non-adherence (OR = 1.61; p-value = 2e-7); this association of SCZ PRS with medication non-adherence was observed both in the EUR (OR = 1.59; p-value = 3e-6) and EAS (OR = 1.73; p-value = 0.035) samples.

# Discussion

This is the first study to assess whether genetic risk for ADHD is associated with lithium response. We found that higher genetic loading for ADHD was associated with less clinical improvement while on lithium using a continuous measure of response. Importantly, our study is also the first to assess the joint impact of multiple PRS on lithium response. We found that while the association of ADHD and MDD PRS remained significant after adjusting for other PRS, the association of the SCZ PRS with response outcomes did not hold after adjusting for the association with ADHD and MDD PRS. Furthermore, our study is the first to investigate the polygenic effects on the Alda B score and found that only the SCZ PRS was associated with the Alda B score, operating through a strong association with non-adherence to taking medication.

These findings are important in light of the clinical and genetic overlap between ADHD and BD. There is a substantial comorbidity of ADHD and BD in adulthood, with ADHD estimated to co-occur in around 9 to 35% of adult patients with BD[(2)](https://paperpile.com/c/J9xJYr/QYfW),[(31–33)](https://paperpile.com/c/J9xJYr/K5od%2BQVYn%2B2MMn) and longitudinal studies showing that approximately 25% of individuals with childhood ADHD develop BD[(34)](https://paperpile.com/c/J9xJYr/3bsK). Furthermore, the symptomatic overlap between the two disorders (e.g. impulsivity, mood swings, sleep difficulties, talkativeness), as well as the similar profile of other psychiatric comorbidities, makes the differential diagnosis challenging[(16)](https://paperpile.com/c/J9xJYr/tzpf),[(35)](https://paperpile.com/c/J9xJYr/9A6O). Finally, genetic studies have shown a small but significant genetic overlap and shared risk genes between BD and ADHD, and suggested that the amount of overlap varies with the age-of-onset of BD[(16–18,36,37)](https://paperpile.com/c/J9xJYr/tzpf%2B7rGw%2BAgtK%2Bmssm%2B5mQ0). Furthermore, prior history of ADHD during childhood and earlier age-of-onset of BD have been associated with worse response to lithium[(15,19)](https://paperpile.com/c/J9xJYr/MXui%2BHHZF). Comorbidity with ADHD also led to lower response rates in children with mania[(38)](https://paperpile.com/c/J9xJYr/Fm5X). In a predictive model for lithium response, ADHD was among the factors with the strongest effect size[(39)](https://paperpile.com/c/J9xJYr/fJ0a). It was also recently shown that lithium was inferior to risperidone in treating prepubertal patients with BD and comorbid ADHD[(40)](https://paperpile.com/c/J9xJYr/776E). These results point toward the fact that the delineation between bipolar disorder with and without ADHD might help define subgroups that respond differently to lithium. Our results show that genetic vulnerability to ADHD might influence lithium response and that ADHD PRS could therefore be used in future studies to stratify clinical populations. It is important to note that because ADHD history was not consistently collected as part of the clinical battery for inclusion in ConLiGen, we were not able to explicitly test for association between ADHD history and lithium response.

It is, however, important to keep in mind that causality cannot be inferred from associations with PRS and that these should therefore be interpreted with caution. Indeed, PRS for ADHD, MDD and SCZ have recently been associated with several subphenotypes in BD[(41–43)](https://paperpile.com/c/J9xJYr/Ir0o%2Brqdt%2BmTEC) and traits in the general population[(44)](https://paperpile.com/c/J9xJYr/aNEZ), which are in turn associated with lithium response[(15,45,46)](https://paperpile.com/c/J9xJYr/HHZF%2Bx6dX%2BhMWd). For instance, PRS for MDD and ADHD are associated with higher BMI[(44)](https://paperpile.com/c/J9xJYr/aNEZ), while lower BMI was associated with better lithium response[(15)](https://paperpile.com/c/J9xJYr/HHZF). Also, SCZ PRS is associated with psychotic features in BD, which have repeatedly been shown to be associated with worse lithium response[(41,46)](https://paperpile.com/c/J9xJYr/Ir0o%2BhMWd). Finally, all three PRS have shown associations with socio-economic traits as well as general and mental health outcomes that might directly or indirectly impact treatment response[(44)](https://paperpile.com/c/J9xJYr/aNEZ). These traits were not systematically collected as part of ConLiGen, and thus were not included in analyses.

To address the question of whether the observed effect of PRS on treatment response was mediated by important confounders for measuring treatment response, we assessed PRS associations with the B score and its components. Somewhat surprisingly, the PRS for ADHD was not associated with any of the components, while the PRS for SCZ showed a strong positive association with non-adherence. This is of particular importance as the association between the SCZ PRS and responder status (Alda Total > 7) seems to be mainly mediated through this association and disappears when analyzing Alda A alone. Furthermore, this result underlines the importance of including potential confounders, in particular treatment adherence, in response scores to better understand causality. While the PRS for SCZ is being extensively studied as a potential predictor for treatment response in several disorders[(13,47,48)](https://paperpile.com/c/J9xJYr/AZo4%2BQ2cE%2BZRIx),[(49,50)](https://paperpile.com/c/J9xJYr/sSjI%2BKdEU), the non-adherence or other confounders are often not studied and could strongly impact the conclusions.

While our data suggests that the relationship between ADHD and lithium response is worth further investigation, these results have limited clinical utility, as the variances explained by each PRS are small. This can partially be explained by the heterogeneity of lithium response in our large multi-center dataset, but also points towards a limitation of current application of PRS. It is probable that treatment models will have to include multiple PRS as well as other types of data (e.g. clinical subphenotypes) to have enough predictive power to be effectively used in clinical practice. This was unfortunately not possible in the current analyses, as deeper phenotypic information is only currently being collected by the consortium. Integration of such data will not only strengthen predictions, but also allow for a better understanding of causality. Indeed, complex relationships such as those between genetic loading for schizophrenia, psychotic events, adherence and responsiveness can only be studied in an integrative way.

In summary, our study shows independent associations between PRS for ADHD and MDD with poorer lithium response, as well as an association between PRS for SCZ and non-adherence to treatment. While being based on the largest collection of lithium response currently available, it is important that these results are replicated in an independent dataset. With larger GWAS becoming available and PRS methods continuing to be refined, incorporating polygenic risk into predictive models may lead to an improved understanding of lithium treatment and, ultimately, to better clinical care.

# Conflict of Interest Statement

Eduard Vieta has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), and the Stanley Medical Research Institute. Michael Bauer has received grants from the Deutsche Forschungsgemeinschaft (DFG), and Bundesministeriums für Bildung und Forschung (BMBF), and served as consultant, advisor or CME speaker for the following entities: Allergan, Aristo, Janssen, Lilly, Lundbeck, neuraxpharm, Otsuka, Sandoz, Servier, and Sunovion outside the submitted work. Sarah Kittel-Schneider has received grants and served as consultant, advisor or speaker for the following entities: Medice Arzneimittel Pütter GmbH and Shire. Bernhard Baune has received grants and served as consultant, advisor or CME speaker for the following entities: AstraZeneca, Bristol-Myers Squibb, Janssen, Lundbeck, Otsuka, Servier, the National Health and Medical Research Council, the Fay Fuller Foundation, the James and Diana Ramsay Foundation. Tadafumi Kato received honoraria for lectures, manuscripts, and/or consultancy, from Kyowa Hakko Kirin Co., Ltd., Eli Lilly Japan K.K., Otsuka Pharmaceutical Co., Ltd., GlaxoSmithKline K.K., Taisho Toyama Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Meiji Seika Pharma Co., Ltd., Pfizer Japan Inc., Mochida Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Janssen Pharmaceutical K.K., Janssen Asia Pacific, Yoshitomiyakuhin, Astellas Pharma Inc., Wako Pure Chemical Industries, Ltd., Wiley Publishing Japan, Nippon Boehringer Ingelheim Co. Ltd., Kanae Foundation for the Promotion of Medical Science, MSD K.K., Kyowa Pharmaceutical Industry Co., Ltd. and Takeda Pharmaceutical Co., Ltd. T.K. also received a research grant from Takeda Pharmaceutical Co., Ltd. Peter Falkai has received grants and served as consultant, advisor or CME speaker for the following entities Abbott, GlaxoSmithKline, Janssen, Essex, Lundbeck, Otsuka, Gedeon Richter, Servier and Takeda as well as the German Ministry of Science and the German Ministry of Health. Eva Reininghaus has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen and Institut Allergosan. Mikael Landén declares that, over the past 36 months, he has received lecture honoraria from Lundbeck and served as scientific consultant for EPID Research Oy; no other equity ownership, profit-sharing agreements, royalties, or patent. Kazufumi Akiyama has received consulting honoraria from Taisho Toyama Pharmaceutical Co., Ltd. The other authors have no other conflict of interest to disclose.

# Statement of Ethics

Research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Each site’s institutional review board approved the study protocol and every participant provided written consent. Further information can be found in the seminal ConLiGen paper (Hou *et al.* 2016).

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# Author Contributions

# Data analysis: BJC, AB, BL. Conceived and/or designed work: BJC, LH, SP, UH, MA-2, MAF, TGS, FJM, JMB. Acquired data: SP, MA, KA, NA, ATA, RA, BA, JA, LB, MB, BTB, FB, AB-2, SB, AB-2, PC, HC, CC, SC, SRC, FC, CC-2, PMC, ND, AD, FD, MD, JD, BÉ, PF, EF, AJF, LF, SG, JSG, FSG, MG, PG, RH, JH, SH, PH, SJ, EJ, JK, LK, TK, JRK, SK, BK, PK, IK, GL, ML, CL, ML-2, SGL, MM, MM-2, LM, MJM, SLM, PBM, MM-2, FMM, PM, CMN, MMN, TN, CO, UO, NO, AP, CP, JBP, AR, ER, MR, GAR, JKR, MS, PRS, KS, BWS, GS, TS, PDS, KS-2, CS, CMS, AS, TS-2, PS, AT, GT, EV, SHW, PPZ, JMF, MA-2, MAF, TGS, FJM, JMB. Interpret results: BJC, VM, JMF, MA-2, MAF, TGS, FJM, JMB. Drafting: BJC, VM, JMB. All authors have contributed to the critical revision of the paper and approved the final version.

# Data Availability Statement

# Data is available through a formal research proposal to the Consortium of Lithium Genetics (<http://www.conligen.org/>).

# References

1. [Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007 May;64(5):543–52.](http://paperpile.com/b/J9xJYr/kCrs)

2. [Merikangas KR, Jin R, He J-P, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011 Mar;68(3):241–51.](http://paperpile.com/b/J9xJYr/QYfW)

3. [Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015 Dec;49(12):1087–206.](http://paperpile.com/b/J9xJYr/7zHU)

4. [Garnham J, Munro A, Slaney C, Macdougall M, Passmore M, Duffy A, et al. Prophylactic treatment response in bipolar disorder: results of a naturalistic observation study. J Affect Disord. 2007 Dec;104(1-3):185–90.](http://paperpile.com/b/J9xJYr/ILGV)

5. [Lähteenvuo M, Tanskanen A, Taipale H, Hoti F, Vattulainen P, Vieta E, et al. Real-world Effectiveness of Pharmacologic Treatments for the Prevention of Rehospitalization in a Finnish Nationwide Cohort of Patients With Bipolar Disorder. JAMA Psychiatry. 2018 Apr 1;75(4):347–55.](http://paperpile.com/b/J9xJYr/3Kjh)

6. [Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N, et al. Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. Lancet. 2016 Mar 12;387(10023):1085–93.](http://paperpile.com/b/J9xJYr/5LzO)

7. [Bauer M, Gitlin M. The Essential Guide to Lithium Treatment [Internet]. 2016. Available from:](http://paperpile.com/b/J9xJYr/sXHE) <http://dx.doi.org/10.1007/978-3-319-31214-9>

8. [Nunes A, Ardau R, Berghöfer A, Bocchetta A, Chillotti C, Deiana V, et al. Prediction of lithium response using clinical data. Acta Psychiatr Scand. 2020 Feb;141(2):131–41.](http://paperpile.com/b/J9xJYr/JeGD)

9. [Ho AM-C, Coombes BJ, Nguyen TTL, Liu D, McElroy SL, Singh B, et al. Mood-Stabilizing Antiepileptic Treatment Response in Bipolar Disorder: A Genome-Wide Association Study. Clin Pharmacol Ther [Internet]. 2020 Jul 5; Available from:](http://paperpile.com/b/J9xJYr/8lEP) <http://dx.doi.org/10.1002/cpt.1982>

10. [Chen C-H, Lee C-S, Lee M-TM, Ouyang W-C, Chen C-C, Chong M-Y, et al. Variant GADL1 and response to lithium therapy in bipolar I disorder. N Engl J Med. 2014 Jan 9;370(2):119–28.](http://paperpile.com/b/J9xJYr/R5hy)

11. [Song J, Bergen SE, Di Florio A, Karlsson R, Charney A, Ruderfer DM, et al. Genome-wide association study identifies SESTD1 as a novel risk gene for lithium-responsive bipolar disorder. Mol Psychiatry. 2017 Aug;22(8):1223.](http://paperpile.com/b/J9xJYr/nB8d)

12. [Jacobs A, Hagin M, Shugol M, Shomron N, Pillar N, Fañanás L, et al. The black sheep of the family- whole-exome sequencing in family of lithium response discordant bipolar monozygotic twins. Eur Neuropsychopharmacol. 2020 May;34:19–27.](http://paperpile.com/b/J9xJYr/xeyN)

13. [International Consortium on Lithium Genetics (ConLi+Gen), Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, et al. Association of Polygenic Score for Schizophrenia and HLA Antigen and Inflammation Genes With Response to Lithium in Bipolar Affective Disorder: A Genome-Wide Association Study. JAMA Psychiatry. 2018 Jan 1;75(1):65–74.](http://paperpile.com/b/J9xJYr/ZRIx)

14. [Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, Cearns M, et al. Association of polygenic score for major depression with response to lithium in patients with bipolar disorder. Mol Psychiatry [Internet]. 2020 Mar 16; Available from:](http://paperpile.com/b/J9xJYr/uZGb) <http://dx.doi.org/10.1038/s41380-020-0689-5>

15. [Hui TP, Kandola A, Shen L, Lewis G, Osborn DPJ, Geddes JR, et al. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. Acta Psychiatr Scand. 2019 Aug;140(2):94–115.](http://paperpile.com/b/J9xJYr/HHZF)

16. [Duffy A. The nature of the association between childhood ADHD and the development of bipolar disorder: a review of prospective high-risk studies. Am J Psychiatry. 2012 Dec;169(12):1247–55.](http://paperpile.com/b/J9xJYr/tzpf)

17. [Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu, Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. Cell. 2019 Dec 12;179(7):1469–82.e11.](http://paperpile.com/b/J9xJYr/7rGw)

18. [O’Connell KS, Shadrin A, Bahrami S, Smeland OB, Bettella F, Frei O, et al. Identification of genetic overlap and novel risk loci for attention-deficit/hyperactivity disorder and bipolar disorder. Mol Psychiatry [Internet]. 2019 Dec 2; Available from:](http://paperpile.com/b/J9xJYr/AgtK) <http://dx.doi.org/10.1038/s41380-019-0613-z>

19. [Strober M, DeAntonio M, Schmidt-Lackner S, Freeman R, Lampert C, Diamond J. Early childhood attention deficit hyperactivity disorder predicts poorer response to acute lithium therapy in adolescent mania. J Affect Disord. 1998 Nov;51(2):145–51.](http://paperpile.com/b/J9xJYr/MXui)

20. [Heilbronner U, Schulze TG. ConLiGen – A consortium investigating the genetic underpinnings of lithium response in bipolar disorder [Internet]. Vol. 172, Annales Médico-psychologiques, revue psychiatrique. 2014. p. 197–8. Available from:](http://paperpile.com/b/J9xJYr/vHe2) <http://dx.doi.org/10.1016/j.amp.2014.02.017>

21. [Scott J, Etain B, Manchia M, Brichant-Petitjean C, Geoffroy PA, Schulze T, et al. An examination of the quality and performance of the Alda scale for classifying lithium response phenotypes. Bipolar Disord [Internet]. 2019 Aug 29; Available from:](http://paperpile.com/b/J9xJYr/InH5) <http://dx.doi.org/10.1111/bdi.12829>

22. [Manchia M, Adli M, Akula N, Ardau R, Aubry J-M, Backlund L, et al. Assessment of Response to Lithium Maintenance Treatment in Bipolar Disorder: A Consortium on Lithium Genetics (ConLiGen) Report. PLoS One. 2013 Jun 19;8(6):e65636.](http://paperpile.com/b/J9xJYr/lGxO)

23. [Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen W-M. Robust relationship inference in genome-wide association studies. Bioinformatics. 2010 Nov 15;26(22):2867–73.](http://paperpile.com/b/J9xJYr/eRXb)

24. [Loh P-R, Danecek P, Palamara PF, Fuchsberger C, A Reshef Y, K Finucane H, et al. Reference-based phasing using the Haplotype Reference Consortium panel. Nat Genet. 2016 Nov;48(11):1443–8.](http://paperpile.com/b/J9xJYr/Ig38)

25. [Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, et al. Next-generation genotype imputation service and methods. Nat Genet. 2016 Oct;48(10):1284–7.](http://paperpile.com/b/J9xJYr/YvHP)

26. [Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019 Jan;51(1):63–75.](http://paperpile.com/b/J9xJYr/XpKc)

27. [Howard DM, Adams MJ, Clarke T-K, Hafferty JD, Gibson J, Shirali M, et al. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nat Neurosci. 2019 Mar;22(3):343–52.](http://paperpile.com/b/J9xJYr/4PvY)

28. [Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014 Jul 24;511(7510):421–7.](http://paperpile.com/b/J9xJYr/p0E8)

29. [Mak TSH, Porsch RM, Choi SW, Zhou X, Sham PC. Polygenic scores via penalized regression on summary statistics. Genet Epidemiol. 2017 Sep;41(6):469–80.](http://paperpile.com/b/J9xJYr/KQpc)

30. [Coombes BJ, Ploner A, Bergen SE, Biernacka JM. A principal component approach to improve association testing with polygenic risk scores. Genet Epidemiol [Internet]. 2020 Jul 21; Available from:](http://paperpile.com/b/J9xJYr/ExrO) <http://dx.doi.org/10.1002/gepi.22339>

31. [Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biol Psychiatry. 2005 Jun 1;57(11):1467–73.](http://paperpile.com/b/J9xJYr/K5od)

32. [Skirrow C, Hosang GM, Farmer AE, Asherson P. An update on the debated association between ADHD and bipolar disorder across the lifespan. J Affect Disord. 2012 Dec 10;141(2-3):143–59.](http://paperpile.com/b/J9xJYr/QVYn)

33. [Sandstrom A, Perroud N, Alda M, Uher R, Pavlova B. Prevalence of attention-deficit/hyperactivity disorder in people with mood disorders: A systematic review and meta-analysis. Acta Psychiatr Scand [Internet]. 2021 Feb 2; Available from:](http://paperpile.com/b/J9xJYr/2MMn) <http://dx.doi.org/10.1111/acps.13283>

34. [Uchida M, Spencer TJ, Faraone SV, Biederman J. Adult Outcome of ADHD: An Overview of Results From the MGH Longitudinal Family Studies of Pediatrically and Psychiatrically Referred Youth With and Without ADHD of Both Sexes. J Atten Disord. 2018 Apr;22(6):523–34.](http://paperpile.com/b/J9xJYr/3bsK)

35. [Marangoni C, De Chiara L, Faedda GL. Bipolar disorder and ADHD: comorbidity and diagnostic distinctions. Curr Psychiatry Rep. 2015 Aug;17(8):604.](http://paperpile.com/b/J9xJYr/9A6O)

36. [Grigoroiu-Serbanescu M, Giaroli G, Thygesen JH, Shenyan O, Bigdeli TB, Bass NJ, et al. Predictive power of the ADHD GWAS 2019 polygenic risk scores in independent samples of bipolar patients with childhood ADHD. J Affect Disord. 2020 Mar 15;265:651–9.](http://paperpile.com/b/J9xJYr/mssm)

37. [van Hulzen KJE, Scholz CJ, Franke B, Ripke S, Klein M, McQuillin A, et al. Genetic Overlap Between Attention-Deficit/Hyperactivity Disorder and Bipolar Disorder: Evidence From Genome-wide Association Study Meta-analysis. Biol Psychiatry. 2017 Nov 1;82(9):634–41.](http://paperpile.com/b/J9xJYr/5mQ0)

38. [State RC, Rosanne C. State, Frye MA, Altshuler LL, Strober M, DeAntonio M, et al. Chart Review of the Impact of Attention-Deficit/Hyperactivity Disorder Comorbidity on Response to Lithium or Divalproex Sodium in Adolescent Mania [Internet]. Vol. 65, The Journal of Clinical Psychiatry. 2004. p. 1057–63. Available from:](http://paperpile.com/b/J9xJYr/Fm5X) <http://dx.doi.org/10.4088/jcp.v65n0805>

39. [Kim TT, Dufour S, Xu C, Cohen ZD, Sylvia L, Deckersbach T, et al. Predictive modeling for response to lithium and quetiapine in bipolar disorder. Bipolar Disord. 2019 Aug;21(5):428–36.](http://paperpile.com/b/J9xJYr/fJ0a)

40. [Vitiello B, Riddle MA, Yenokyan G, Axelson DA, Wagner KD, Joshi P, et al. Treatment Moderators and Predictors of Outcome in the Treatment of Early Age Mania (TEAM) Study [Internet]. Vol. 51, Journal of the American Academy of Child & Adolescent Psychiatry. 2012. p. 867–78. Available from:](http://paperpile.com/b/J9xJYr/776E) <http://dx.doi.org/10.1016/j.jaac.2012.07.001>

41. [Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Electronic address: douglas.ruderfer@vanderbilt.edu, Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. Cell. 2018 Jun 14;173(7):1705–15.e16.](http://paperpile.com/b/J9xJYr/Ir0o)

42. [Coombes BJ, Markota M, John Mann J, Colby C, Stahl E, Talati A, et al. Dissecting clinical heterogeneity of bipolar disorder using multiple polygenic risk scores [Internet]. Vol. 10, Translational Psychiatry. 2020. Available from:](http://paperpile.com/b/J9xJYr/rqdt) <http://dx.doi.org/10.1038/s41398-020-00996-y>

43. [Markota M, Coombes BJ, Larrabee BR, McElroy SL, Bond DJ, Veldic M, et al. Association of schizophrenia polygenic risk score with manic and depressive psychosis in bipolar disorder. Transl Psychiatry. 2018 Sep 10;8(1):188.](http://paperpile.com/b/J9xJYr/mTEC)

44. [Leppert B, Millard LAC, Riglin L, Davey Smith G, Thapar A, Tilling K, et al. A cross-disorder PRS-pheWAS of 5 major psychiatric disorders in UK Biobank. PLoS Genet. 2020 May;16(5):e1008185.](http://paperpile.com/b/J9xJYr/aNEZ)

45. [Grof P, Alda M, Grof E, Zvolsky P, Walsh M. Lithium response and genetics of affective disorders. J Affect Disord. 1994 Oct;32(2):85–95.](http://paperpile.com/b/J9xJYr/x6dX)

46. [Nunes A, Stone W, Ardau R, Berghöfer A, Bocchetta A, Chillotti C, et al. Exemplar scoring identifies genetically separable phenotypes of lithium responsive bipolar disorder. Transl Psychiatry. 2021 Jan 11;11(1):36.](http://paperpile.com/b/J9xJYr/hMWd)

47. [Zhang J-P, Robinson D, Yu J, Gallego J, Fleischhacker WW, Kahn RS, et al. Schizophrenia Polygenic Risk Score as a Predictor of Antipsychotic Efficacy in First-Episode Psychosis. Am J Psychiatry. 2019 Jan 1;176(1):21–8.](http://paperpile.com/b/J9xJYr/AZo4)

48. [Fanelli G, Benedetti F, Kasper S, Zohar J, Souery D, Montgomery S, et al. Higher polygenic risk scores for schizophrenia may be suggestive of treatment non-response in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2020 Nov 9;110170.](http://paperpile.com/b/J9xJYr/Q2cE)

49. [Santoro ML, Ota V, de Jong S, Noto C, Spindola LM, Talarico F, et al. Polygenic risk score analyses of symptoms and treatment response in an antipsychotic-naive first episode of psychosis cohort [Internet]. Vol. 8, Translational Psychiatry. 2018. Available from:](http://paperpile.com/b/J9xJYr/sSjI) <http://dx.doi.org/10.1038/s41398-018-0230-7>

50. [Gasse C, Wimberley T, Wang Y, Mors O, Børglum A, Als TD, et al. Schizophrenia polygenic risk scores, urbanicity and treatment-resistant schizophrenia. Schizophr Res. 2019 Oct;212:79–85.](http://paperpile.com/b/J9xJYr/KdEU)

**Figure Legends**

**Table 1.** Summary of Alda scores distributions in the full sample and by ancestry (EUR or EAS).

**Fig. 1.** PRS effect sizes with each outcome (**a)** = A score or **b)** = non-responder) meta-analysis in either a model with each PRS included by itself (black) or in a joint model with all PRS (red). Confidence intervals shown are Bonferroni corrected. P-values are shown on the right from either the model with each PRS by itself (P.m) or in the joint model (P.j).

**Fig. 2.** Independent PRS associations with Alda B score and each component for the full meta-analysis. Bars indicate -log10(p-value) and direction of association. Dashed lines are drawn at p-value = 0.01.