Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Title page

Title: Association between polygenic risk scores and outcome of electroconvulsive therapy

Robert Sigström, MD, PhD*[1, 2], Kaarina Kowalec, PhD*[3, 4], Lina Jonsson, PhD[1], Caitlin C Clements, PhD[3, 5], Robert Karlsson, PhD[3], Axel Nordenskjöld, MD, PhD [6], Erik Pålsson, PhD[1], Patrick F Sullivan, MD[3, 7, 8], Mikael Landén, MD, PhD [1, 3]

*Co-first author

[1]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

[2]Department of Cognition and Old Age Psychiatry, Sahlgrenska University Hospital, Gothenburg, Sweden

[3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[4]College of Pharmacy, University of Manitoba, Winnipeg, Canada

[5]Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA

[6]University Health Care Research Centre, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

[7]Department of Genetics, University of North Carolina, Chapel Hill, NC, USA

[8]Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

Corresponding author:

Robert Sigström

University of Gothenburg,

Institute of Neuroscience and Physiology

Blå stråket 15

SE 413 45 Gothenburg, Sweden.

Telephone: +46 31 343 98 59

E-mail: robert.sigstrom@gu.se

Manuscript word count: 3370

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Disclosure:

Dr Sullivan is a consultant for and shareholder in Neumora Therapeutics. Dr Landén and Dr Nordenskjöld has received lecture honoraria from Lundbeck Pharmaceutical. Dr Sigström, Dr Kowalec, Dr Jonsson, Dr Clements, Dr Karlsson, Dr Nordenskjöld, and Dr Pålsson report no financial relationships with commercial interest.

Acknowledgements

This work was supported by grants from the Swedish Research Council (2018-02653, 2018-05973 to ML), the Swedish Foundation for Strategic Research (KF10-0039 to ML), and by the Swedish state under the agreement between the Swedish Government and the county councils, the ALF-agreement (ALFGBG-716801 to ML). Dr Sigström was supported by a grant from the Swedish state under the agreement between the Swedish Government and the county councils, the ALF-agreement (ALFGBG-942684). Dr Kowalec was supported by a grant from the University of Manitoba and National Institutes of Mental Health (R01MH123724). Dr Sullivan was supported by a grant from Swedish Research Council (Vetenskapsrådet, award D0886501). Dr Landén was supported by a grant from the Wenner-Gren foundation (SSv2019-0008).

We thank the study participants for their contribution to this research. We also thank the staff at ECT units throughout Sweden and the Swedish National Quality register for ECT (Q-ECT) for collection and sharing of data; the BBMRI.se and KI Biobank at Karolinska Institutet for their biobank service. A special thanks to the PREFECT project manager Anders Juréus, the PREFECT research nurses Marie Lundin, Birgitta Ohlander, Milka Krestelica, Radja Dawoud, Martina Wennberg, and PREFECT data manager Bozenna Illiadou. The computations/data handling was enabled by resources provided by the Swedish National Infrastructure for Computing (SNIC) at Uppsala University.

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Abstract

Objective: Identifying biomarkers associated with response to electroconvulsive therapy (ECT) may aid clinical decisions. We examined whether increasing polygenic liabilities for major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SCZ) are associated with improvement following ECT for a major depressive episode.

Methods: Between 2013 and 2017, patients who had at least one treatment series recorded in the Swedish National Quality Register for ECT were invited to provide a blood sample for genotyping. The present study included 2,320 participants (median age 51 years; 62.8% women) who had received an ECT series for a major depressive episode (77.1% unipolar depression), had a registered treatment outcome, and whose polygenic risk scores (PRS) could be calculated. We estimated the effect of PRS on Clinical Global Impression-Improvement (CGI-Improvement) after each ECT series using ordinal logistic regressions.

Results: Increasing PRS for MDD was associated with less CGI-Improvement (OR=0.89 per standard deviation [SD], 95%CI=0.82–0.96, r^2=0.4%, p=0.002), and increasing PRS for BD was associated with more CGI-Improvement (OR per SD=1.14, 95%CI=1.05–1.23, r^2=0.5%, p=0.001) after ECT. PRS for SCZ was not associated with improvement. In an overlapping sample (N=1207) with data on response and remission derived from the self-rated version of the MADRS scale, results were similar except that PRS-SCZ was also associated with remission.

Conclusions: Improvement after ECT is associated with polygenic liability for MDD and BD, providing evidence of a genetic component for ECT clinical response. These liabilities may be considered along with clinical predictors in future prediction models of ECT outcomes.

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Introduction

Electroconvulsive therapy (ECT) is an effective treatment for major depressive episodes (MDEs) with remission rates of 60–75% in modern clinical trials(1, 2). Most patients respond to ECT in clinical practice and pragmatic trials, but remission rates are lower (30–50%)(3-5). Identifying biomarkers associated with improvement after ECT may facilitate the clinical decision to prescribe ECT.

It has long been thought that ECT is most effective for patients with a severe, episodic, heritable, and possibly 'biological' type of depression(6, 7), but the evidence is limited. In a meta-analysis of 34 studies, symptom severity predicted quantitative response but was negatively associated with qualitative remission(8). As for other severity measures, psychotic features predict response and remission but results for melancholic features have been inconclusive, partly due to definitional variation(2, 8). Notably, ECT is similarly effective in unipolar and bipolar depression(9, 10). Bipolar disorder (BD) has a higher estimated heritability than major depressive disorder (MDD)(11), but we recently showed that the single nucleotide polymorphism (SNP)-based heritability of ECT-treated depression is considerably higher (29–34%) than that of mild-moderate depression (6.5–8.0%)(12), suggesting that more heritable 'biological' depression is more likely to be treated with ECT.

Polygenic risk scores (PRS) are quantitative measures of the polygenic liability for complex traits, calculated from the summary statistics of genome-wide association studies (GWAS)(13). Although PRS are not yet sufficiently predictive to inform clinical decisions, polygenic liabilities for psychiatric disorders have been associated with response to specific therapeutics(14-18). A recent study of 266 MDE patients found that increasing PRS for schizophrenia (SCZ) was associated with greater improvement after ECT, even among patients without clinical psychotic features (19). The notion that ECT works best in more heritable forms of MDE also suggests that improvement after ECT might be associated with

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

increased polygenic liability for MDD and bipolar disorder (BD), the two disorders for which ECT is recommended as a treatment for a severe MDE(20).

The aim of the present study was to investigate if therapeutic response following ECT for MDE is associated with PRS for MDD, BD, and SCZ. To this end, we analyzed a large cohort of Swedish patients who had received ECT for an MDE.

Methods

Study population

The study population is derived from the Predictors for ECT (PREFECT) study conducted in Sweden(12). Recruitment occurred between 2013–2017. Study participants had received at least one acute ECT series registered in the Swedish National Quality Register for ECT (Q-ECT, http://ect.registercentrum.se). Q-ECT was launched nationally in Sweden in 2011, although some hospitals started registration in 2008. As of 2014, Q-ECT covered 89% of all ECT series in Sweden(20). Local hospital staff routinely enter data on each treatment series into the register via a web-based platform.

The study sample has been described previously(12, 21). Briefly, a letter of invitation was sent to patients ≥ 18 years old registered in Q-ECT. Those who volunteered to participate completed a telephone interview and donated blood that was sent via overnight mail to Karolinska Institutet Biobank. Additional participants were prospectively recruited at eight Swedish hospitals prior to receiving ECT for an MDE. Blood samples were stored in -20°C pending shipment to Karolinska Institutet Biobank for DNA extraction and long-term storage. A total of 2,880 participants provided DNA and had received at least one acute ECT treatment series for an MDE. After exclusion of participants whose genotyping failed quality control (N=40), genetic ancestral outliers (N=138), and those with no registered primary outcome in Q-ECT (N=382), we categorized the remaining 2,320 eligible participants into two groups as previously described(12): The *broad group* included participants with an MDE occurring in the context of (a) a unipolar depressive disorder (International Classification of

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Diseases [ICD], version 10 codes F32-F33, F412, F530), (b) bipolar disorder (F31), (c) another severe mood disorder with pretreatment self-rated Montgomery-Åsberg Depression Rating Scale score (MADRS-S) ≥20 (mixed anxiety and depressive disorder, F41.2; schizoaffective disorder, F25.9; or mood disorder not otherwise specified, F34.9), or (d) MDE as indicated by free text, or a pretreatment MADRS-S ≥20 if the specific indication for treatment was missing. The *narrow group* consisted of the subset who received ECT for an MDE in the context of a unipolar depressive episode only. Psychotic features were considered as present if the indication for ECT was coded with any of the following ICD-10 codes: F323: F333, F315 and F259, or if the indication in free text implied delusions and/or hallucinations.

All participants provided written informed consent. The study was approved by the regional ethical review board in Stockholm (approval nos. 2012/1969-31/1 and 2020-10151).

Outcome measures

Participants could have several registered treatment series in Q-ECT (Table 1). Here, outcome data were captured from the first or only ECT treatment series. Our primary outcome measure was the Clinical Global Impressions of Improvement score (CGI-I)(22) rated immediately after the ECT series. We chose CGI-I as it had the lowest proportion of missing information. CGI-I was available for the first registered treatment series of 92.8% (N=2,154) participants. CGI-I ranges from 1 (very much improved) to 7 (very much worse) and was treated as an ordinal variable. Secondary outcomes were response and remission according to the self-rated MADRS-S(23). MADRS-S was available both pre- and post-treatment for 52.0% (N=1,207) of the sample, of which 79.2% (N=956) provided MADRS-S ratings at their first registered treatment series. The MADRS-S includes 9 items rated from 0–6 (maximum score=54), which correspond to the items in the observer-rated MADRS except ‘apparent sadness’. Response was defined as ≥50% MADRS-S score reduction from pre- to post-treatment. Remission was defined as a post-treatment MADRS-S rating ≤10.

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

A subset of 1052 participants had both MADRS-S and CGI-I data available from the same treatment series. There was a moderate correlation between CGI-I and MADRS-S response (Spearman's ρ=0.48, p<0.001) and MADRS-S remission (Spearman's ρ=0.42, p<0.001).

ECT procedure

ECT was administered using bidirectional, constant-current, brief-pulse devices from Mecta (Mecta Corp, Lake Oswego, Oregon, USA) or Thymatron (Somatics Inc Lake Buff, Illinois, USA). Propofol or thiopental was used for anesthesia. Suxamethonium was used for muscle relaxation. Seizure time was registered with electroencephalography. From Q-ECT, we retrieved data on electrode placement (bilateral or right unilateral at first or last ECT), and charge (mC), and pulse width (categorized into 0.25–49 ms, 0.5 ms, and 0.51–1.20 ms) used at the first session of each treatment series. All participating clinics administered ECT three times per week: Monday, Wednesday, and Friday.

Genotype quality control and imputation

Genotype quality control (QC) and imputation have been described in detail previously(12). Briefly, DNA was extracted from peripheral blood and samples were genotyped on the Illumina GSA-MD SNP array (version GSAMD-24v1-0_20011747_A1) at Life & Brain GmbH (Bonn, Germany). Standard QC was applied using the PGC RICOPILI pipeline(24). All potential samples were included in QC, but the final association analysis was performed on the phenotyped subsets outlined above that passed QC. Samples were excluded (N=40) for: genotype missingness >0.02 (after first filtering SNPs with call rate <0.95), genotypic sex ambiguous or not matching phenotypic data, or autosomal heterozygosity |F| >0.2. SNPs were excluded for: call rate <0.99, difference in missingness between cases and controls >0.005, minor allele frequency <0.01, or deviating from Hardy-Weinberg equilibrium in cases or controls ($P<10^{-6}$). Ancestry outliers were identified by projecting study samples on principal components with respect to 1000 Genomes Project data (phase 3 v5)(25). Individuals further than 3 standard deviations from the European reference population mean for PC1 or PC2 were excluded (N=138) and then the principal components were regenerated for use in the

study analyses as covariates to capture residual confounding by genetic ancestry. Potentially related individuals were identified and one from each pair was flagged for exclusion (estimated identity-by-descent sharing >0.2). Samples passing QC were imputed using the Haplotype Reference Consortium (HRC) r1.1 reference panel on the Sanger Imputation Service using Eagle2 and Positional burrows wheeler transform (PBWF) for phasing and imputation(26). The genome build was hg19.

Polygenic risk score generation

PRS were calculated for MDD and BD using discovery GWAS summary statistics from the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/download-results/) based on large GWAS for each phenotype [MDD: 'mdd2019edinborough'(27); BD: 'bip2019'(28); SCZ: 'scz2022'(29)]. Although the PREFECT sample has not been included in any previous GWAS, we nevertheless removed all Swedish samples from the GWAS summary statistics to reduce the possibility of spurious associations.

PRS were generated for the PREFECT samples as the sum of the risk allele scores, weighted by their effect size in the discovery samples. We performed linkage disequilibrium clumping (r^2<0.1 in 1-Mb windows) on any overlapping SNPs with the 1000 Genomes Project European samples for the reference (phase 3 v5) (25). PRS were calculated using PLINK version 1.9 (30). PRS were coded as risk increasing and standardized to a mean=0 and standard deviation (SD)=1 for interpretability. To reduce the number of comparisons, we used the PRS calculated at the $P_T \leq 0.05$ as exposures in our main analyses, in alignment with previous research(31). Supplementary table 1 contains the details on the number of SNPs used in the calculation of each PRS.

Statistical analysis

We present the descriptive characteristics of the sample using frequency (percent, %) or median (interquartile range, IQR). Our primary analyses investigated the associations of PRS for MDD, BD and SCZ with CGI-I. We used a multivariable proportional odds ordinal logistic regression model adjusting for the first five genetic ancestry principal components. To

facilitate interpretation, we reversed the CGI-I values such that odds ratios (ORs) >1 represent improvement. We also examined the association between quintiles of each PRS and CGI-I, using the lowest quintile as the reference, in multivariable ordinal logistic regressions, given that higher values of PRS may carry greater risks. We conducted approximate likelihood-ratio tests to examine violation of the proportional odds assumption. For the secondary analyses of the association between each PRS and MADRS-S remission and response (defined above), we used multivariable logistic regression analyses adjusted for MADRS-S prior to ECT, and the first five genetic ancestry principal components. We present all results as ORs with 95% confidence intervals (95%CI). For all analyses, we calculated the proportion of variance explained by each PRS as the difference between the Nagelkerke's pseudo-R^2 of the full multivariable model and that of a model excluding the PRS.

We performed four sensitivity analyses of the primary outcome (CGI-I). First, we repeated the analyses for the subset of participants with a narrowly defined MDE. Second, we repeated the analyses using PRS calculated based on alternative p-value inclusion thresholds ($P_T \leq$ 5E-8, 1E-5, 1E-3, 0.01, 0.1, 0.5, 1.0). Finally, we repeated the analysis separately for participants with unilateral electrode placement only vs. bilateral at first or last ECT, and in participants with vs. without psychotic features.

We applied a two-tailed Bonferroni adjusted significance level (p=0.05/3=0.017) in our primary analyses involving CGI-I due to the analyses of three PRS. In our secondary and sensitivity analyses, which were exploratory, we applied the uncorrected statistical significance level (p<0.05). We used SPSS version 26 (IBM corp., Armonk, NY, USA) for data management and STATA version 16 (Stata corp., College Station, TX, USA) for statistical analyses. Figures were produced in *R* version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) using *ggplot2* version 3.3.3(32).

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Results

Sample characteristics

We included 2,320 European genetic ancestry individuals in the primary outcome analysis (CGI-I) (Table 1). The median age was 51 years, 62.8% were women, and 77.1% had an MDE in the context of a MDD (i.e., belonged to the narrowly defined group). The median CGI-I rating after ECT was 2 (corresponding to 'much improved'). The distribution of CGI-I ratings is displayed in Supplementary figure 1.

Primary outcome

Inheritance of a greater burden of common, risk-increasing genetic variants associated with MDD (PRS-MDD) was significantly and *negatively* associated with improvement after ECT (CGI-I, OR for improvement=0.89 per SD, 95%CI=0.82–0.96, p=0.002, Nagelkerke's r^2=0.4%, Figure 1A and Supplementary Table 2). Participants in the highest quintile of PRS-MDD had 31% lower odds of improvement compared to those with the lowest burden (quintile 5 vs. 1, OR=0.69, 95%CI=0.54–0.87, p=0.002, Figure 2A and Supplementary table 3).

Higher PRS-BD was significantly and *positively* associated with improvement after ECT (OR per SD=1.14, 95%CI=1.05–1.23, p=0.003, Nagelkerke's r^2=0.5%). Participants in the highest quintile for genetic burden of BD had 37% higher odds for improvement after ECT than those with the lowest (quintile 5 vs. 1, OR=1.44, 95%CI=1.13–1.84, p=0.003, Figure 2B and Supplementary table 3). PRS-SCZ was not associated with improvement after ECT (OR per SD=1.04, 95% CI=0.97-1.14, p=0.247). All models using PRS as a continuous variable met the proportional odds assumption, but not those of PRS-MDD and BD quintiles, which hence should be interpreted with caution (Supplementary table 3). In a post-hoc analysis, we also found that a PRS (at $P_T \leq 0.05$) of percentage improvement on antidepressants (33) was not associated with improvement following ECT (Supplementary table 4).

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Secondary outcomes

For the MADRS-S analysis, 1,207 participants were eligible. Participant characteristics were similar to the CGI-I sample: 64% were female and 67.5% belonged to the narrowly defined group (an MDE in the context of MDD, Table 1). After ECT, 60.1% (N=725) met the criterion for response (Table 1). Similar to the primary analysis, higher PRS-MDD was associated with lower odds of response (OR per SD 0.85, 95% CI 0.76-0.96, p=0.008, Nagelkerke's r^2=0.8%, Figure 1B and Supplementary table 2), while PRS-BD was associated with higher odds for response (OR per SD 1.13, 95% CI 1.00-1.27, p=0.044, Nagelkerke's r^2=0.4%). PRS-SCZ was not associated with response (OR per SD 1.05, 95% CI 0.93-1.19, p=0.401).

In the MADRS-S sample, 40.1% (N=484) met the criterion for remission after ECT. Higher PRS-MDD was associated with lower odds of remission (OR per SD 0.83, 95% CI=0.73–0.94, Nagelkerke's r^2=1.0%, p=0.002, Figure 1C and Supplementary table 2), while PRS-BD was associated with higher odds for remission (OR per SD 1.15, 95% CI 1.02–1.29, p=0.023, Nagelkerke's r^2=0.6%), as was PRS-SCZ (OR per SD 1.16, 95% CI 1.02–1.31, p=0.020, Nagelkerke's r^2=0.6%).

Sensitivity analyses

We repeated the primary analyses restricting the sample to participants with narrowly defined MDE in the context of MDD and obtained similar results (Figures 1-2, Supplementary tables 2-3). The results were not sensitive to the choice of P_T (Supplementary figure 1). Results were similar to the primary analysis in participants with unilateral electrode placement, but in the limited subsample treated with bilateral electrode placement (N=306), only PRS-MDD was associated with improvement (Supplementary table 5). Among participants without psychotic features, results were similar to the main analysis (Supplementary table 6). No significant effect of any PRS was observed among those with psychotic features (N=348), although point estimates were similar to the primary analysis.

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Discussion

We investigated if improvement after ECT was associated with polygenic liability for MDD and BD in a cohort of 2,320 patients with MDE. We found that higher polygenic liability for MDD was associated with *lower* chance of improvement after ECT, whereas higher polygenic liability for BD was associated with *higher* chance of improvement. In our primary analysis, we could not replicate the relatively strong association between increasing PRS-SCZ and more improvement reported from a previous smaller study (19), although we did find that PRS-SCZ was positively associated with remission according to MADRS-S. In our study, the proportions of participants who received bilateral ECT and who had psychotic features were considerably smaller than in the previous study. But our sensitivity analysis did not suggest that associations between PRS and improvement differed by these factors.

There is a small but growing literature on PRS and therapeutics for mood disorders. PRS-MDD and PRS-SCZ have been associated with lower likelihood of lithium response in bipolar disorder patients(14, 15), while PRS-BD had no such association(18). No robust associations have been found with PRS for psychiatric disorders and response to antidepressants(34-36): Nominal associations of PRS-MDD with less improvement on citalopram/escitalopram(35) or esketamine in treatment-resistant MDD(36) did not survive correction for multiple testing. PRS-MDD was not associated with outcome after cognitive-behavioral therapy for MDE(31). It is noteworthy that higher PRS-MDD has been associated with poorer response to antidepressant treatments rather than the opposite. Higher PRS-MDD has been related to more severe MDD(37), which in turn is believed to predict response to ECT(6, 8). But the measures of depression severity that have been associated with higher PRS-MDD—early age of onset, higher symptom count, and a chronic/unremitting course of illness(37)—do not necessarily correspond to severity as measured by the sum score on symptom scales, which has been used to index severity as a predictor of response to ECT(8). In fact, younger age at treatment and longer duration of current depressive episode (i.e., chronic illness) have previously been associated with poorer response to ECT(8, 10).

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

In contradistinction to PRS-MDD, we found that higher polygenic liability for BD was associated with a better response to ECT. The discrepancy between PRS-MDD and PRS-BD is noteworthy as the efficacy of ECT does not differ between bipolar and unipolar depression(9, 10). Importantly, the association was similar or more pronounced among the subset of patients with unipolar depression.

We have previously reported higher PRS-BD in patients with a severe MDE treated with ECT than in patients with more moderate depression treated with internet-based cognitive behavioral therapy (12). Higher PRS-BD might hence reflect a genetic liability to develop not only bipolar disorder but also more severe depression. Our findings indicate that high polygenic liability for BD might also be associated with response to biological treatments including ECT. Further research is needed to confirm this.

The effect sizes of PRS in this study are small, which echoes other genetic studies of response to psychiatric treatments(14-16). Although effect sizes may increase with larger genomic studies(38), the power of PRS to explain treatment effects might be limited in cohorts with similar phenotypes and relatively small variations in treatment outcome. Also, the genetic correlation between MDD and BD seems to be due to pleiotropic genetic variants, meaning that genetic risk for BD cannot be used to delineate MDD subgroups(39). Thus, PRS of BD and MDD may not be suitable for identification of a subgroup of ‘super responders' to ECT. The genetics of ECT response may also overlap with the genetics of phenotypes associated with poor ECT response, such as personality disorders and substance use(5). Indeed, the genetic architecture of categorically defined psychiatric disorders might differ from that of treatment response. These possibilities should be addressed by further studies, and ultimately by a GWAS of response to ECT, which is an objective of the International Consortium on the Genetics of ECT and Severe Depressive Disorder (GenECT-IC) aiming to recruit 30,000 participants (40).

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Strengths and limitations

The strengths of this study include the large and well-characterized sample with data on treatment outcomes after ECT. Further, the direction and magnitude of effects were consistent between the primary outcome CGI-I and the secondary MADRS-S measures. Sensitivity analyses provided further convergent evidence. Limitations of the study include, first, that data was collected in routine clinical practice, limiting quality supervision. This probably adds noise compared with controlled studies. Second, MADRS-S is self-rated while CGI-I is observer rated, which may explain why CGI-I and MADRS-S were only moderately correlated. Moreover, MADRS-S ratings were missing for more than half of the participants, primarily prior to ECT. This is likely explained by the poor mental state that precluded completing a self-rated instrument and might bias the results by excluding severely ill patients who are expected to respond well to treatment. However, this bias should not affect the results regarding the observer-rated CGI-I. Third, we had limited data on factors known to predict the outcome of ECT, such as duration of the current episode and non-response to antidepressant medication (10). It remains to be examined to what extent the association between, for example, PRS for MDD and treatment outcome, is independent of these variables. Last, given that our sample size was <4,000, the study were neither powered for a GWAS of ECT outcomes, nor for computing heritability estimates for the studied outcomes (41).

Conclusions

We found that response to ECT is associated with lower genetic burden for major depressive disorder and higher genetic burden for bipolar disorder. Yet, the predictive power of the studied polygenic risk scores to predict outcome after ECT was small. It remains to be studied whether polygenic risk scores alongside clinical or demographic factors might add predictive value beyond known clinical predictors of response to ECT.

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

References

1. Kellner CH, Husain MM, Knapp RG, McCall WV, Petrides G, Rudorfer MV, Young RC, Sampson S, McClintock SM, Mueller M, Prudic J, Greenberg RM, Weiner RD, Bailine SH, Rosenquist PB, Raza A, Kaliora S, Latoussakis V, Tobias KG, Briggs MC, Liebman LS, Geduldig ET, Teklehaimanot AA, Lisanby SH, Group CPW. Right unilateral ultrabrief pulse ECT in geriatric depression: phase 1 of the PRIDE study. The American Journal of Psychiatry. 2016;173:1101-1109.

2. Fink M. What was learned: studies by the consortium for research in ECT (CORE) 1997-2011. Acta Psychiatrica Scandinavica. 2014;129:417-426.

3. Semkovska M, Landau S, Dunne R, Kolshus E, Kavanagh A, Jelovac A, Noone M, Carton M, Lambe S, McHugh C, McLoughlin DM. Bitemporal Versus High-Dose Unilateral Twice-Weekly Electroconvulsive Therapy for Depression (EFFECT-Dep): A Pragmatic, Randomized, Non-Inferiority Trial. The American Journal of Psychiatry. 2016;173:408-417.

4. Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA. Effectiveness of electroconvulsive therapy in community settings. Biological Psychiatry. 2004;55:301-312.

5. Brus O, Cao Y, Gustafsson E, Hultén M, Landen M, Lundberg J, Nordanskog P, Nordenskjöld A. Self-assessed remission rates after electroconvulsive therapy of depressive disorders. European Psychiatry. 2017;45:154-160.

6. Kellner CH, Popeo DM, Pasculli RM, Briggs MC, Gamss S. Appropriateness for electroconvulsive therapy (ECT) can be assessed on a three-item scale. Medical hypotheses. 2012;79:204-206.

7. Hickie I, Mason C, Parker G, Brodaty H. Prediction of ECT response: validation of a refined sign-based (CORE) system for defining melancholia. The British Journal of Psychiatry. 1996;169:68-74.

8. van Diermen L, van den Ameele S, Kamperman AM, Sabbe BCG, Vermeulen T, Schrijvers D, Birkenhager TK. Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. Br J Psychiatry. 2018;212:71-80.

9. Dierckx B, Heijnen WT, van den Broek WW, Birkenhäger TK. Efficacy of electroconvulsive therapy in bipolar versus unipolar major depression: a meta-analysis. Bipolar disorders. 2012;14:146-150.

10. Haq AU, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ. Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. J Clin Psychiatry. 2015;76:1374-1384.

11. Wray N, Gottesman I. Using Summary Data from the Danish National Registers to Estimate Heritabilities for Schizophrenia, Bipolar Disorder, and Major Depressive Disorder. Frontiers in genetics. 2012;3.

12. Clements CC, Karlsson R, Lu Y, Juréus A, Rück C, Andersson E, Boberg J, Pedersen NL, Bulik CM, Nordenskjöld A, Pålsson E, Sullivan PF, Landén M. Genome-wide association study of patients with a severe major depressive episode treated with electroconvulsive therapy. Molecular Psychiatry. 2021.

13. Murray GK, Lin T, Austin J, McGrath JJ, Hickie IB, Wray NR. Could Polygenic Risk Scores Be Useful in Psychiatry?: A Review. JAMA Psychiatry. 2021;78:210-219.

14. Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, Cearns M, Heilbronner U, Degenhardt F, Tekola-Ayele F, Hsu Y-H, Shekhtman T, Adli M, Akula N, Akiyama K, Ardau R, Arias B, Aubry J-M, Backlund L, Bhattacharjee AK, Bellivier F, Benabarre A, Bengesser S, Biernacka JM, Birner A, Brichant-Petitjean C, Cervantes P, Chen H-C, Chillotti C, Cichon S, Cruceanu C, Czerski PM, Dalkner N, Dayer A, Del Zompo M, DePaulo JR, Étain B, Jamain S, Falkai P, Forstner AJ, Frisen L, Frye MA, Fullerton JM, Gard S, Garnham JS, Goes FS, Grigoroiu-Serbanescu M, Grof P, Hashimoto R, Hauser J, Herms S, Hoffmann P, Hofmann A, Jiménez E, Kahn J-P, Kassem L, Kuo P-H, Kato T, Kelsoe JR, Kittel-Schneider S, Kliwicki S, König B, Kusumi I, Laje G, Landén M, Lavebratt C, Leboyer M, Leckband SG, Tortorella A, Manchia M, Martinsson L, McCarthy MJ, McElroy SL, Colom F, Mitjans M, Mondimore FM, Monteleone P, Nievergelt CM, Nöthen MM, Novák T, O'Donovan C, Ozaki N, Ösby U, Pfennig A, Potash JB, Reif A, Major Depressive Disorder Working Group of the Psychiatric Genomics C, Reininghaus E, Rouleau GA, Rybakowski JK, Schalling M, Schofield PR, Schweizer BW, Severino G, Shilling PD, Shimoda K, Simhandl C, Slaney CM, Squassina A, Stamm T, Stopkova P, Maj M, Turecki G, Vieta E, Veeh J, Witt SH, Wright A, Zandi PP, Mitchell PB, Bauer M, Alda M, Rietschel M, McMahon FJ, Schulze TG, Baune BT. Association of polygenic score for major depression with response to lithium in patients with bipolar disorder. Molecular Psychiatry. 2020;26:2457-2470.

15. Amare AT, Schubert KO, Hou L, Clark SR, Papiol S, Heilbronner U, Degenhardt F, Tekola-Ayele F, Hsu Y-H, Shekhtman T. 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;75:65-74.

16. Zhang J-P, Robinson D, Yu J, Gallego J, Fleischhacker WW, Kahn RS, Crespo-Facorro B, Vazquez-Bourgon J, Kane JM, Malhotra AK, Lencz T. Schizophrenia Polygenic Risk Score as a Predictor of Antipsychotic Efficacy in First-Episode Psychosis. The American Journal of Psychiatry. 2019;176:21-28.

17. Andersson E, Crowley JJ, Lindefors N, Ljotsson B, Hedman-Lagerlof E, Boberg J, El Alaoui S, Karlsson R, Lu Y, Mattheisen M, Kahler AK, Svanborg C, Mataix-Cols D, Mattsson S, Forsell E, Kaldo V, Schalling M, Lavebratt C, Sullivan PF, Ruck C. Genetics of response to cognitive behavior therapy in adults with major depression: a preliminary report. Mol Psychiatry. 2019;24:484-490.

18. Schubert KO, Thalamuthu A, Amare AT, Frank J, Streit F, Adl M, Akula N, Akiyama K, Ardau R, Arias B, Aubry J-M, Backlund L, Bhattacharjee AK, Bellivier F, Benabarre A, Bengesser S, Biernacka JM, Birner A, Marie-Claire C, Cearns M, Cervantes P, Chen H-C, Chillotti C, Cichon S, Clark SR, Cruceanu C, Czerski PM, Dalkner N, Dayer A, Degenhardt F, Del Zompo M, Depaulo JR, Étain B, Falkai P, Forstner AJ, Frisen L, Frye MA, Fullerton JM, Gard S, Garnham JS, Goes FS, Grigoroiu-Serbanescu M, Grof P, Hashimoto R, Hauser J, Heilbronner U, Herms S, Hoffmann P, Hou L, Hsu Y-H, Jamain S, Jiménez E, Kahn J-P, Kassem L, Kuo P-H, Kato T, Kelsoe J, Kittel-Schneider S, Ferensztajn-Rochowiak E, König B, Kusumi I, Laje G, Landén M, Lavebratt C, Leboyer M, Leckband SG, Maj M, Manchia M, Martinsson L, McCarthy MJ, McElroy S, Colom F, Mitjans M, Mondimore FM, Monteleone P, Nievergelt CM, Nöthen MM, Novák T, O'Donovan C, Ozaki N, Ösby U, Papiol S, Pfennig A, Pisanu C, Potash JB, Reif A, Reininghaus E, Rouleau GA, Rybakowski JK, Schalling M, Schofield PR, Schweizer BW, Severino G, Shekhtman T, Shilling PD, Shimoda K, Simhandl C, Slaney CM, Squassina A, Stamm T, Stopkova P, Tekola-Ayele F, Tortorella A, Turecki G, Veeh J, Vieta E, Witt SH, Roberts G, Zandi PP, Alda M, Bauer M, McMahon FJ, Mitchell PB, Schulze TG, Rietschel M, Baune BT. Combining schizophrenia and depression polygenic risk scores improves the genetic prediction of lithium response in bipolar disorder patients. Translational psychiatry. 2021;11.

19. Luykx JJ, Loef D, Lin B, Van Diermen L, Nuninga JO, Van Exel E, Oudega ML, Rhebergen D, Schouws SNTM, Van Eijndhoven P, Verwijk E, Schrijvers D, Birkenhager TK, Ryan KM, Arts B, Van Bronswijk SC, Kenis G, Schurgers G, Baune BT, Arns M, Van Dellen EE, Somers M, Sommer IEC, Boks MP, Gülöksüz S, McLoughlin DM, Dols A, Rutten BPF. Interrogating Associations Between Polygenic Liabilities and Electroconvulsive Therapy Effectiveness. Biological Psychiatry. 2022;91:531-539.

20. Nordanskog P, Hultén M, Landén M, Lundberg J, von Knorring L, Nordenskjöld A. Electroconvulsive therapy in sweden 2013: data from the national quality register for ECT. The Journal of ECT. 2015;31:263-267.

21. Sigström R, Nordenskjöld A, Juréus A, Clements C, Joas E, Pålsson E, Landén M. Long-term subjective memory after electroconvulsive therapy. BJPsych Open. 2020;6:e26.

22. Guy W: Clinical global impression. in ECDEU assessment manual for psychopharmacology. Rockville, MD, National Institute of Mental Health; 1976. pp. 217-221.

23. Svanborg P, Åsberg M. A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Åsberg Depression Rating Scale (MADRS). Journal of affective disorders. 2001;64:203-216.

24. Lam M, Awasthi S, Watson HJ, Goldstein J, Panagiotaropoulou G, Trubetskoy V, Karlsson R, Frei O, Fan C-C, De Witte W, Mota NR, Mullins N, Brügger K, Lee SH, Wray NR, Skarabis N, Huang H, Neale B, Daly MJ, Mattheisen M, Walters R, Ripke S. RICOPILI: rapid imputation for consortias pipeline. Bioinformatics (Oxford, England). 2020;36:930-933.

25. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR. A global reference for human genetic variation. Nature. 2015;526:68-74.

26. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, Kang HM, Fuchsberger C, Danecek P, Sharp K, Luo Y, Sidore C, Kwong A, Timpson N, Koskinen S, Vrieze S, Scott LJ, Zhang H, Mahajan A, Veldink J, Peters U, Pato C, van Duijn CM, Gillies CE, Gandin I, Mezzavilla M, Gilly A, Cocca M, Traglia M, Angius A, Barrett JC, Boomsma D, Branham K, Breen G, Brummett CM, Busonero F, Campbell H, Chan A, Chen S, Chew E, Collins FS, Corbin LJ, Smith GD, Dedoussis G, Dorr M, Farmaki A-E, Ferrucci L, Forer L, Fraser RM, Gabriel S, Levy S, Groop L, Harrison T, Hattersley A, Holmen OL, Hveem K, Kretzler M, Lee JC, McGue M, Meitinger T, Melzer D, Min JL, Mohlke KL, Vincent JB, Nauck M, Nickerson D, Palotie A, Pato M, Pirastu N, McInnis M, Richards JB, Sala C, Salomaa V, Schlessinger D, Schoenherr S, Slagboom PE, Small K, Spector T, Stambolian D, Tuke M, Tuomilehto J, Van den Berg LH, Van Rheenen W, Volker U, Wijmenga C, Toniolo D, Zeggini E, Gasparini P, Sampson MG, Wilson JF, Frayling T, de Bakker PIW, Swertz MA, McCarroll S, Kooperberg C, Dekker A, Altshuler D, Willer C, Iacono W, Ripatti S, Soranzo N, Walter K, Swaroop A, Cucca F, Anderson CA, Myers RM, Boehnke M, McCarthy MI, Durbin R, Haplotype Reference C. A reference panel of 64,976 haplotypes for genotype imputation. Nature genetics. 2016;48:1279-1283.

27. Howard DM, Adams MJ, Clarke T-K, Hafferty JD, Gibson J, Shirali M, Coleman JRI, Hagenaars SP, Ward J, Wigmore EM, Alloza C, Shen X, Barbu MC, Xu EY, Whalley HC, Marioni RE, Porteous DJ, Davies G, Deary IJ, Hemani G, Berger K, Teismann H, Rawal R, Arolt V, Baune BT, Dannlowski U, Domschke K, Tian C, Hinds DA, andMe Research T, Major Depressive Disorder Working Group of the Psychiatric Genomics C, Trzaskowski M, Byrne EM, Ripke S, Smith DJ, Sullivan PF, Wray NR, Breen G, Lewis CM, McIntosh AM. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. Nature neuroscience. 2019;22:343-352.

28. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetskoy V, Mattheisen M, Wang Y, Coleman JRI, Gaspar HA, de Leeuw CA, Steinberg S, Pavlides JMW, Trzaskowski M, Byrne EM, Pers TH, Holmans PA, Richards AL, Abbott L, Agerbo E, Akil H, Albani D, Alliey-Rodriguez N, Als TD, Anjorin A, Antilla V, Awasthi S, Badner JA, Baekvad-Hansen M, Barchas JD, Bass N, Bauer M, Belliveau R, Bergen SE, Pedersen CB, Boen E, Boks MP, Boocock J, Budde M, Bunney W, Burmeister M, Bybjerg-Grauholm J, Byerley W, Casas M, Cerrato F, Cervantes P, Chambert K, Charney AW, Chen D, Churchhouse C, Clarke TK, Coryell W, Craig DW, Cruceanu C, Curtis D, Czerski PM, Dale AM, de Jong S, Degenhardt F, Del-Favero J, DePaulo JR, Djurovic S, Dobbyn AL, Dumont A, Elvsashagen T, Escott-Price V, Fan CC, Fischer SB, Flickinger M, Foroud TM, Forty L,

Frank J, Fraser C, Freimer NB, Frisen L, Gade K, Gage D, Garnham J, Giambartolomei C, Pedersen MG, Goldstein J, Gordon SD, Gordon-Smith K, Green EK, Green MJ, Greenwood TA, Grove J, Guan W, Guzman-Parra J, Hamshere ML, Hautzinger M, Heilbronner U, Herms S, Hipolito M, Hoffmann P, Holland D, Huckins L, Jamain S, Johnson JS, Jureus A, Kandaswamy R, Karlsson R, Kennedy JL, Kittel-Schneider S, Knowles JA, Kogevinas M, Koller AC, Kupka R, Lavebratt C, Lawrence J, Lawson WB, Leber M, Lee PH, Levy SE, Li JZ, Liu C, Lucae S, Maaser A, MacIntyre DJ, Mahon PB, Maier W, Martinsson L, McCarroll S, McGuffin P, McInnis MG, McKay JD, Medeiros H, Medland SE, Meng F, Milani L, Montgomery GW, Morris DW, Muhleisen TW, Mullins N, Nguyen H, Nievergelt CM, Adolfsson AN, Nwulia EA, O'Donovan C, Loohuis LMO, Ori APS, Oruc L, Osby U, Perlis RH, Perry A, Pfennig A, Potash JB, Purcell SM, Regeer EJ, Reif A, Reinbold CS, Rice JP, Rivas F, Rivera M, Roussos P, Ruderfer DM, Ryu E, Sanchez-Mora C, Schatzberg AF, Scheftner WA, Schork NJ, Shannon Weickert C, Shehktman T, Shilling PD, Sigurdsson E, Slaney C, Smeland OB, Sobell JL, Soholm Hansen C, Spijker AT, St Clair D, Steffens M, Strauss JS, Streit F, Strohmaier J, Szelinger S, Thompson RC, Thorgeirsson TE, Treutlein J, Vedder H, Wang W, Watson SJ, Weickert TW, Witt SH, Xi S, Xu W, Young AH, Zandi P, Zhang P, Zollner S, Adolfsson R, Agartz I, Alda M, Backlund L, Baune BT, Bellivier F, Berrettini WH, Biernacka JM, Blackwood DHR, Boehnke M, Borglum AD, Corvin A, Craddock N, Daly MJ, Dannlowski U, Esko T, Etain B, Frye M, Fullerton JM, Gershon ES, Gill M, Goes F, Grigoroiu-Serbanescu M, Hauser J, Hougaard DM, Hultman CM, Jones I, Jones LA, Kahn RS, Kirov G, Landen M, Leboyer M, Lewis CM, Li QS, Lissowska J, Martin NG, Mayoral F, McElroy SL, McIntosh AM, McMahon FJ, Melle I, Metspalu A, Mitchell PB, Morken G, Mors O, Mortensen PB, Muller-Myhsok B, Myers RM, Neale BM, Nimgaonkar V, Nordentoft M, Nothen MM, O'Donovan MC, Oedegaard KJ, Owen MJ, Paciga SA, Pato C, Pato MT, Posthuma D, Ramos-Quiroga JA, Ribases M, Rietschel M, Rouleau GA, Schalling M, Schofield PR, Schulze TG, Serretti A, Smoller JW, Stefansson H, Stefansson K, Stordal E, Sullivan PF, Turecki G, Vaaler AE, Vieta E, Vincent JB, Werge T, Nurnberger JI, Wray NR, Di Florio A, Edenberg HJ, Cichon S, Ophoff RA, Scott LJ, Andreassen OA, Kelsoe J, Sklar P. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nature genetics. 2019;51:793-803.

29. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, Bryois J, Chen CY, Dennison CA, Hall LS, Lam M, Watanabe K, Frei O, Ge T, Harwood JC, Koopmans F, Magnusson S, Richards AL, Sidorenko J, Wu Y, Zeng J, Grove J, Kim M, Li Z, Voloudakis G, Zhang W, Adams M, Agartz I, Atkinson EG, Agerbo E, Al Eissa M, Albus M, Alexander M, Alizadeh BZ, Alptekin K, Als TD, Amin F, Arolt V, Arrojo M, Athanasiu L, Azevedo MH, Bacanu SA, Bass NJ, Begemann M, Belliveau RA, Bene J, Benyamin B, Bergen SE, Blasi G, Bobes J, Bonassi S, Braun A, Bressan RA, Bromet EJ, Bruggeman R, Buckley PF, Buckner RL, Bybjerg-Grauholm J, Cahn W, Cairns MJ, Calkins ME, Carr VJ, Castle D, Catts SV, Chambert KD, Chan RCK, Chaumette B, Cheng W, Cheung EFC, Chong SA, Cohen D, Consoli A, Cordeiro Q, Costas J, Curtis C, Davidson M, Davis KL, de Haan L, Degenhardt F, DeLisi LE, Demontis D, Dickerson F, Dikeos D, Dinan T, Djurovic S, Duan J, Ducci G, Dudbridge F, Eriksson JG, Fañanás L, Faraone SV, Fiorentino A, Forstner A, Frank J, Freimer NB, Fromer M, Frustaci A, Gadelha A, Genovese G, Gershon ES, Giannitelli M, Giegling I, Giusti-Rodríguez P, Godard S, Goldstein JI, González Peñas J, González-Pinto A, Gopal S, Gratten J, Green MF, Greenwood TA, Guillin O, Gülöksüz S, Gur RE, Gur RC, Gutiérrez B, Hahn E, Hakonarson H, Haroutunian V, Hartmann AM, Harvey C, Hayward C, Henskens FA, Herms S, Hoffmann P, Howrigan DP, Ikeda M, Iyegbe C, Joa I, Julià A, Kähler AK, Kam-Thong T, Kamatani Y, Karachanak-Yankova S, Kebir O, Keller MC, Kelly BJ, Khrunin A, Kim SW, Klovins J, Kondratiev N, Konte B, Kraft J, Kubo M, Kučinskas V, Kučinskiene ZA, Kusumawardhani A, Kuzelova-Ptackova H, Landi S, Lazzeroni LC, Lee PH, Legge SE, Lehrer DS, Lencer R, Lerer B, Li M, Lieberman J, Light GA, Limborska S, Liu CM, Lönnqvist J, Loughland CM, Lubinski J, Luykx JJ, Lynham A, Macek M, Jr., Mackinnon A, Magnusson PKE, Maher BS, Maier W, Malaspina D, Mallet J, Marder SR, Marsal S, Martin AR, Martorell L, Mattheisen M, McCarley RW, McDonald C, McGrath JJ, Medeiros H, Meier S, Melegh B, Melle I, Mesholam-Gately RI, Metspalu A, Michie PT, Milani L, Milanova V, Mitjans M, Molden E, Molina E, Molto MD, Mondelli V, Moreno C, Morley CP, Muntané G, Murphy KC, Myin-Germeys I, Nenadić I, Nestadt G, Nikitina-Zake L, Noto C, Nuechterlein KH, O'Brien NL, O'Neill FA, Oh SY, Olincy A, Ota VK, Pantelis C, Papadimitriou GN, Parellada M, Paunio T, Pellegrino R, Periyasamy S, Perkins DO, Pfuhlmann B, Pietiläinen O, Pimm J, Porteous D, Powell J, Quattrone D, Quested D, Radant AD, Rampino A, Rapaport MH, Rautanen A, Reichenberg A, Roe C, Roffman JL, Roth J, Rothermundt M, Rutten BPF, Saker-Delye S, Salomaa V, Sanjuan J, Santoro ML, Savitz A, Schall U, Scott RJ, Seidman LJ, Sharp SI, Shi J, Siever LJ, Sigurdsson E, Sim K, Skarabis N, Slominsky P, So HC, Sobell JL, Söderman E, Stain HJ, Steen NE, Steixner-Kumar AA, Stögmann E,

Stone WS, Straub RE, Streit F, Strengman E, Stroup TS, Subramaniam M, Sugar CA, Suvisaari J, Svrakic DM, Swerdlow NR, Szatkiewicz JP, Ta TMT, Takahashi A, Terao C, Thibaut F, Toncheva D, Tooney PA, Torretta S, Tosato S, Tura GB, Turetsky BI, Üçok A, Vaaler A, van Amelsvoort T, van Winkel R, Veijola J, Waddington J, Walter H, Waterreus A, Webb BT, Weiser M, Williams NM, Witt SH, Wormley BK, Wu JQ, Xu Z, Yolken R, Zai CC, Zhou W, Zhu F, Zimprich F, Atbaşoğlu EC, Ayub M, Benner C, Bertolino A, Black DW, Bray NJ, Breen G, Buccola NG, Byerley WF, Chen WJ, Cloninger CR, Crespo-Facorro B, Donohoe G, Freedman R, Galletly C, Gandal MJ, Gennarelli M, Hougaard DM, Hwu HG, Jablensky AV, McCarroll SA, Moran JL, Mors O, Mortensen PB, Müller-Myhsok B, Neil AL, Nordentoft M, Pato MT, Petryshen TL, Pirinen M, Pulver AE, Schulze TG, Silverman JM, Smoller JW, Stahl EA, Tsuang DW, Vilella E, Wang SH, Xu S, Adolfsson R, Arango C, Baune BT, Belangero SI, Børglum AD, Braff D, Bramon E, Buxbaum JD, Campion D, Cervilla JA, Cichon S, Collier DA, Corvin A, Curtis D, Forti MD, Domenici E, Ehrenreich H, Escott-Price V, Esko T, Fanous AH, Gareeva A, Gawlik M, Gejman PV, Gill M, Glatt SJ, Golimbet V, Hong KS, Hultman CM, Hyman SE, Iwata N, Jönsson EG, Kahn RS, Kennedy JL, Khusnutdinova E, Kirov G, Knowles JA, Krebs MO, Laurent-Levinson C, Lee J, Lencz T, Levinson DF, Li QS, Liu J, Malhotra AK, Malhotra D, McIntosh A, McQuillin A, Menezes PR, Morgan VA, Morris DW, Mowry BJ, Murray RM, Nimgaonkar V, Nöthen MM, Ophoff RA, Paciga SA, Palotie A, Pato CN, Qin S, Rietschel M, Riley BP, Rivera M, Rujescu D, Saka MC, Sanders AR, Schwab SG, Serretti A, Sham PC, Shi Y, St Clair D, Stefánsson H, Stefansson K, Tsuang MT, van Os J, Vawter MP, Weinberger DR, Werge T, Wildenauer DB, Yu X, Yue W, Holmans PA, Pocklington AJ, Roussos P, Vassos E, Verhage M, Visscher PM, Yang J, Posthuma D, Andreassen OA, Kendler KS, Owen MJ, Wray NR, Daly MJ, Huang H, Neale BM, Sullivan PF, Ripke S, Walters JTR, O'Donovan MC. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022.

30. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. GigaScience. 2015;4.

31. Andersson E, Crowley JJ, Lindefors N, Ljótsson B, Hedman-Lagerlöf E, Boberg J, El Alaoui S, Karlsson R, Lu Y, Mattheisen M, Kähler AK, Svanborg C, Mataix-Cols D, Mattsson S, Forsell E, Kaldo V, Schalling M, Lavebratt C, Sullivan PF, Rück C. Genetics of response to cognitive behavior therapy in adults with major depression: a preliminary report. Molecular Psychiatry. 2019;24:484-490.

32. Wickham H: Elegant Graphics for Data Analysis. New York, Springer Verlag; 2016.

33. Pain O, Hodgson K, Trubetskoy V, Ripke S, Marshe VS, Adams MJ, Byrne EM, Campos AI, Carrillo-Roa T, Cattaneo A, Als TD, Souery D, Dernovsek MZ, Fabbri C, Hayward C, Henigsberg N, Hauser J, Kennedy JL, Lenze EJ, Lewis G, Müller DJ, Martin NG, Mulsant BH, Mors O, Perroud N, Porteous DJ, Rentería ME, Reynolds CF, Rietschel M, Uher R, Wigmore EM, Maier W, Wray NR, Aitchison KJ, Arolt V, Baune BT, Biernacka JM, Bondolfi G, Domschke K, Kato M, Li QS, Liu Y-L, Serretti A, Tsai S-J, Turecki G, Weinshilboum R, Kasper S, Zohar J, Souery D, Montgomery S, Albani D, Forloni G, Ferentinos P, Rujescu D, Mendlewicz J, Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TFM, Bacanu S-A, Bækvad-Hansen M, Beekman ATF, Bigdeli TB, Binder EB, Bryois J, Buttenschøn HN, Bybjerg-Grauholm J, Cai N, Castelao E, Christensen JH, Clarke T-K, Coleman JRI, Colodro-Conde L, Couvy-Duchesne B, Craddock N, Crawford GE, Davies G, Deary IJ, Degenhardt F, Derks EM, Direk N, Dolan CV, Dunn EC, Eley TC, Escott-Price V, Hassan Kiadeh FF, Finucane HK, Foo JC, Forstner AJ, Frank J, Gaspar HA, Gill M, Goes FS, Gordon SD, Grove J, Hall LS, Hansen CS, Hansen TF, Herms S, Hickie IB, Hoffmann P, Homuth G, Horn C, Hottenga J-J, Hougaard DM, Howard DM, Ising M, Jansen R, Jones I, Jones LA, Jorgenson E, Knowles JA, Kohane IS, Kraft J, Kretzschmar WW, Kutalik Z, Li Y, Lind PA, MacIntyre DJ, MacKinnon DF, Maier RM, Maier W, Marchini J, Mbarek H, McGrath P, McGuffin P, Medland SE, Mehta D, Middeldorp CM, Mihailov E, Milaneschi Y, Milani L, Mondimore FM, Montgomery GW, Mostafavi S, Mullins N, Nauck M, Ng B, Nivard MG, Nyholt DR, O'Reilly PF, Oskarsson H, Owen MJ, Painter JN, Pedersen CB, Pedersen MG, Peterson RE, Peyrot WJ, Pistis G, Posthuma D, Quiroz JA, Qvist P, Rice JP, Riley BP, Rivera M, Mirza SS, Schoevers R, Schulte EC, Shen L, Shi J, Shyn SI, Sigurdsson E, Sinnamon GCB, Smit JH, Smith DJ, Stefansson H, Steinberg S, Streit F, Strohmaier J, Tansey KE, Teismann H, Teumer A, Thompson W, Thomson PA, Thorgeirsson TE, Traylor M, Treutlein J, Trubetskoy V, Uitterlinden AG, Umbricht D, Van der Auwera S, van Hemert AM, Viktorin A, Visscher PM, Wang Y, Webb BT, Weinsheimer SM, Wellmann J, Willemsen G, Witt

SH, Wu Y, Xi HS, Yang J, Zhang F, Arolt V, Baune BT, Berger K, Boomsma DI, Cichon S, Dannlowski U, de Geus EJC, DePaulo JR, Domenici E, Domschke K, Esko T, Grabe HJ, Hamilton SP, Hayward C, Heath AC, Kendler KS, Kloiber S, Lewis G, Li QS, Lucae S, Madden PAF, Magnusson PK, Martin NG, McIntosh AM, Metspalu A, Mors O, Mortensen PB, Müller-Myhsok B, Nordentoft M, Nöthen MM, O'Donovan MC, Paciga SA, Pedersen NL, Penninx BWJH, Perlis RH, Porteous DJ, Potash JB, Preisig M, Rietschel M, Schaefer C, Schulze TG, Smoller JW, Stefansson K, Tiemeier H, Uher R, Völzke H, Weissman MM, Werge T, Lewis CM, Levinson DF, Breen G, Børglum AD, Sullivan PF, McIntosh AM, Lewis CM. Identifying the Common Genetic Basis of Antidepressant Response. Biological Psychiatry Global Open Science. 2021.

34. García-González J, Tansey KE, Hauser J, Henigsberg N, Maier W, Mors O, Placentino A, Rietschel M, Souery D, Žagar T, Czerski PM, Jerman B, Buttenschøn HN, Schulze TG, Zobel A, Farmer A, Aitchison KJ, Craig I, McGuffin P, Giupponi M, Perroud N, Bondolfi G, Evans D, O'Donovan M, Peters TJ, Wendland JR, Lewis G, Kapur S, Perlis R, Arolt V, Domschke K, Major Depressive Disorder Working Group of the Psychiatric Genomic C, Breen G, Curtis C, Sang-Hyuk L, Kan C, Newhouse S, Patel H, Baune BT, Uher R, Lewis CM, Fabbri C. Pharmacogenetics of antidepressant response: A polygenic approach. Progress in neuro-psychopharmacology & biological psychiatry. 2017;75:128-134.

35. Ward J, Graham N, Strawbridge RJ, Ferguson A, Jenkins G, Chen W, Hodgson K, Frye M, Weinshilboum R, Uher R, Lewis CM, Biernacka J, Smith DJ. Polygenic risk scores for major depressive disorder and neuroticism as predictors of antidepressant response: Meta-analysis of three treatment cohorts. PLoS One. 2018;13:e0203896.

36. Li QS, Wajs E, Ochs-Ross R, Singh J, Drevets WC. Genome-wide association study and polygenic risk score analysis of esketamine treatment response. Scientific reports. 2020;10:12649.

37. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, Adams MJ, Agerbo E, Air TM, Andlauer TMF, Bacanu S-A, Bækvad-Hansen M, Beekman AFT, Bigdeli TB, Binder EB, Blackwood DRH, Bryois J, Buttenschøn HN, Bybjerg-Grauholm J, Cai N, Castelao E, Christensen JH, Clarke T-K, Coleman JIR, Colodro-Conde L, Couvy-Duchesne B, Craddock N, Crawford GE, Crowley CA, Dashti HS, Davies G, Deary IJ, Degenhardt F, Derks EM, Direk N, Dolan CV, Dunn EC, Eley TC, Eriksson N, Escott-Price V, Kiadeh FHF, Finucane HK, Forstner AJ, Frank J, Gaspar HA, Gill M, Giusti-Rodríguez P, Goes FS, Gordon SD, Grove J, Hall LS, Hannon E, Hansen CS, Hansen TF, Herms S, Hickie IB, Hoffmann P, Homuth G, Horn C, Hottenga J-J, Hougaard DM, Hu M, Hyde CL, Ising M, Jansen R, Jin F, Jorgenson E, Knowles JA, Kohane IS, Kraft J, Kretzschmar WW, Krogh J, Kutalik Z, Lane JM, Li Y, Li Y, Lind PA, Liu X, Lu L, MacIntyre DJ, MacKinnon DF, Maier RM, Maier W, Marchini J, Mbarek H, McGrath P, McGuffin P, Medland SE, Mehta D, Middeldorp CM, Mihailov E, Milaneschi Y, Milani L, Mill J, Mondimore FM, Montgomery GW, Mostafavi S, Mullins N, Nauck M, Ng B, Nivard MG, Nyholt DR, O'Reilly PF, Oskarsson H, Owen MJ, Painter JN, Pedersen CB, Pedersen MG, Peterson RE, Pettersson E, Peyrot WJ, Pistis G, Posthuma D, Purcell SM, Quiroz JA, Qvist P, Rice JP, Riley BP, Rivera M, Saeed Mirza S, Saxena R, Schoevers R, Schulte EC, Shen L, Shi J, Shyn SI, Sigurdsson E, Sinnamon GBC, Smit JH, Smith DJ, Stefansson H, Steinberg S, Stockmeier CA, Streit F, Strohmaier J, Tansey KE, Teismann H, Teumer A, Thompson W, Thomson PA, Thorgeirsson TE, Tian C, Traylor M, Treutlein J, Trubetskoy V, Uitterlinden AG, Umbricht D, Van der Auwera S, van Hemert AM, Viktorin A, Visscher PM, Wang Y, Webb BT, Weinsheimer SM, Wellmann J, Willemsen G, Witt SH, Wu Y, Xi HS, Yang J, Zhang F, eQtlgen, andMe, Arolt V, Baune BT, Berger K, Boomsma DI, Cichon S, Dannlowski U, de Geus ECJ, DePaulo JR, Domenici E, Domschke K, Esko T, Grabe HJ, Hamilton SP, Hayward C, Heath AC, Hinds DA, Kendler KS, Kloiber S, Lewis G, Li QS, Lucae S, Madden PFA, Magnusson PK, Martin NG, McIntosh AM, Metspalu A, Mors O, Mortensen PB, Müller-Myhsok B, Nordentoft M, Nöthen MM, O'Donovan MC, Paciga SA, Pedersen NL, Penninx BWJH, Perlis RH, Porteous DJ, Potash JB, Preisig M, Rietschel M, Schaefer C, Schulze TG, Smoller JW, Stefansson K, Tiemeier H, Uher R, Völzke H, Weissman MM, Werge T, Winslow AR, Lewis CM, Levinson DF, Breen G, Børglum AD, Sullivan PF, Major Depressive Disorder Working Group of the Psychiatric Genomics C. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nature genetics. 2018;50:668-681.

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

38. Fullerton JM, Nurnberger JI. Polygenic risk scores in psychiatry: Will they be useful for clinicians? F1000Res. 2019;8.

39. Howard DM, Folkersen L, Coleman JRI, Adams MJ, Glanville K, Werge T, Hagenaars SP, Han B, Porteous D, Campbell A, Clarke T-K, Breen G, Sullivan PF, Wray NR, Lewis CM, McIntosh AM. Genetic stratification of depression in UK Biobank. Translational psychiatry. 2020;10:163.

40. Soda T, McLoughlin DM, Clark SR, Oltedal L, Kessler U, Haavik J, Bousman C, Smith DJ, Bioque M, Clements CC, Loo C, Vila-Rodriguez F, Minelli A, Mickey BJ, Milev R, Docherty AR, Langan Martin J, Achtyes ED, Arolt V, Redlich R, Dannlowski U, Cardoner N, Clare E, Craddock N, Di Florio A, Dmitrzak-Weglarz M, Forty L, Gordon-Smith K, Husain M, Ingram WM, Jones L, Jones I, Juruena M, Kirov G, Landén M, Müller DJ, Nordensköld A, Pålsson E, Paul M, Permoda A, Pliszka B, Rea J, Schubert KO, Sonnen JA, Soria V, Stageman W, Takamiya A, Urretavizacaya M, Watson S, Zavorotny M, Young AH, Vieta E, Rybakowski JK, Gennarelli M, Zandi PP, Sullivan PF, Baune BT. International Consortium on the Genetics of Electroconvulsive Therapy and Severe Depressive Disorders (Gen-ECT-ic). European Archives of Psychiatry and Clinical Neuroscience. 2020;270:921-932.

41. Zaitlen N, Kraft P. Heritability in the genome-wide association era. Human genetics. 2012;131:1655-1664.

Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

Figure legends

Figure 1. Association between polygenic risk scores and measures of improvement after ECT

LEGEND: The figure shows the associations between PRS for MDD, BD, and SCZ and outcomes of ECT among all participants (main analysis) and among only those with unipolar depression (sensitivity analysis). Odds ratios (OR) are per standard deviation (SD) of increasing PRS and an OR >1 = higher odds of favorable outcome. The bars represent 95% confidence intervals. The x-axis is logarithmic. **Panel A:** Associations with the primary outcome, CGI-I (Clinical Global Impressions-Improvement; N_{all}=2,320, N_{narrow}=1,789). Estimated from an ordinal logistic regression model adjusted for the first five genetic ancestry principal components. **Panels B and C:** Associations between MADRS-S (Self-rated Montgomery-Åsberg Depression Rating Scale; N_{all}=1,207, N_{narrow}=815) and response (B) and remission (C), estimated from binary logistic regression models adjusted for MADRS-S before ECT, and the first five genetic ancestry principal components.

Figure 2. Associations between quintiles of PRS and CGI improvement after ECT.

LEGEND: The figure shows the odds of more improvement after ECT according to CGI-I for each quintile of polygenic risk score relative to the 1st quintile (N_{all}=2,320, N_{narrow}=1,789). The bars represent 95% confidence intervals. Estimated from ordinal logistic regression models adjusted for the first five genetic ancestry principal components. The x-axis is logarithmic. **Panel A:** PRS-MDD. **Panel B:** PRS-BD. **Panel C:** PRS-SCZ.

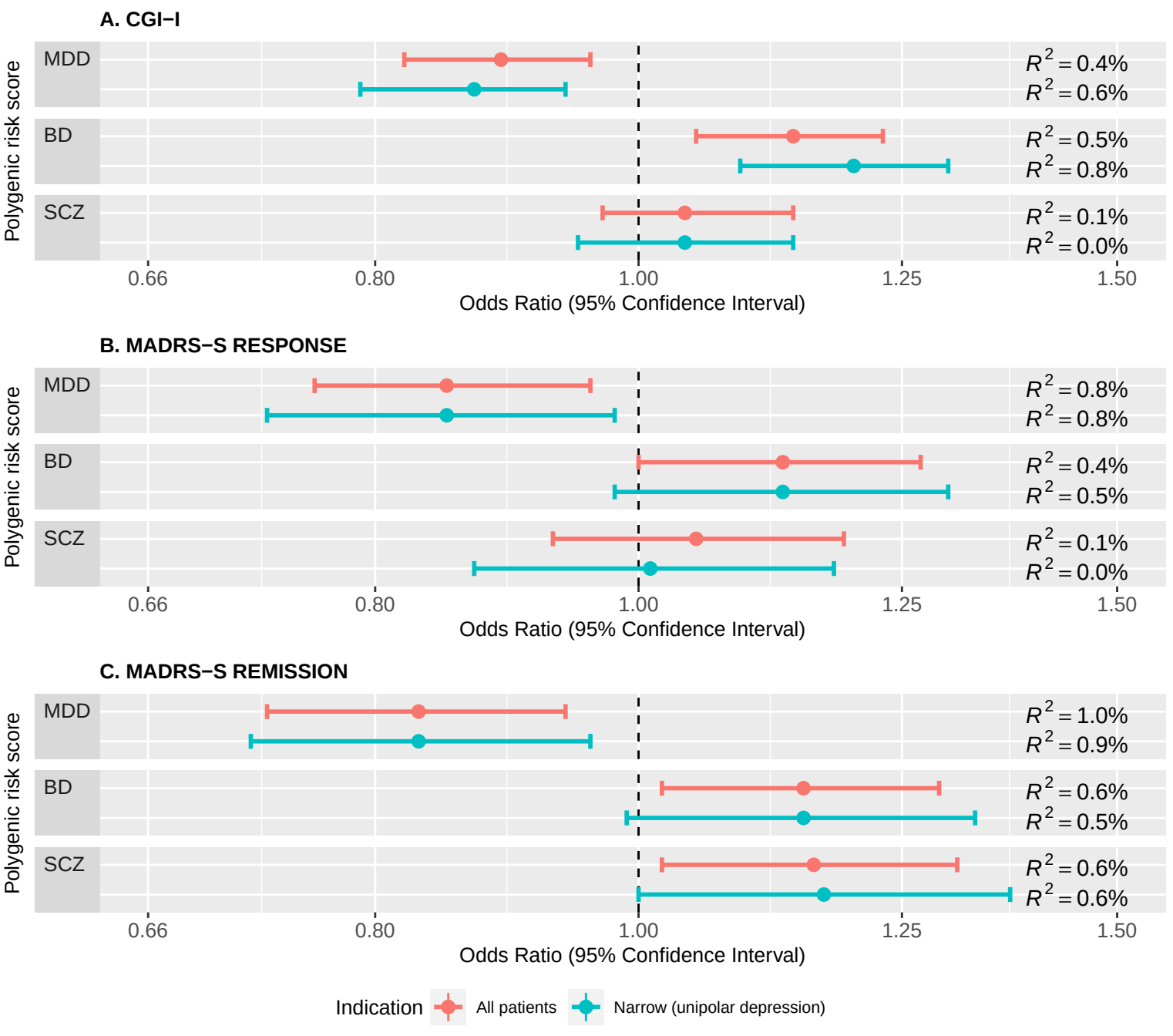
Accepted version of manuscript published in The American Journal of Psychiatry, Vol. 179, Issue 11, Pages 844-852, doi: 10.1176/appi.ajp.22010045

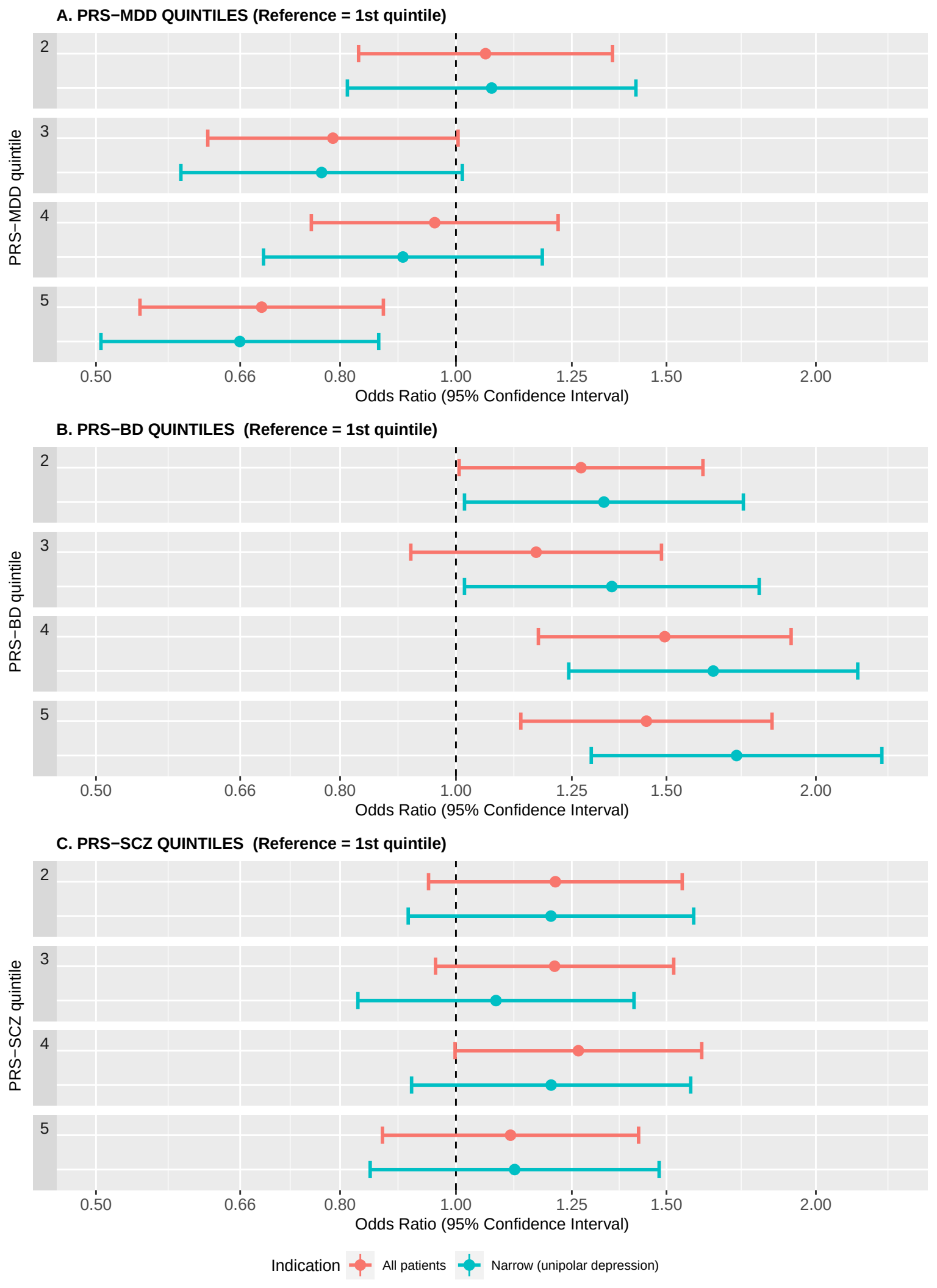
Table 1. Characteristics of participants

	CGI-I sample (N=2,320)[a]			MADRS-S sample (N=1,207)[a]		
	N or median	% or IQR	Missing	N or median	% or IQR	Missing
Female sex	1,456	62.8%	0	772	64.0%	0
Indication			0			0
Narrow (unipolar depression)	1,789	77.1%		815	67.5%	
Broad (all other indications)	531	22.9%		392	32.5%	
Psychotic features	348	15.0%		133	11.0%	
Age (years)	51	37-64	0	51	37-64	
No. of acute treatment series registered in Q-ECT			0			0
1	1,309	56.4%		556	46.1%	
2	531	22.9%		300	24.9%	
3 or more (maximum 19)	480	20.7%		351	29.1%	
MADRS-S before ECT	34	28-40	1,135	34	28-40	0
MADRS-S after ECT	13	6-21	1,049	14	7-22	0
CGI-I after ECT	2	1-2	0	2	1-2	195
No. of ECT sessions	8	6-10	0	8	6-10	0
Electrode placement at first or last ECT			2			1
Unilateral	2,012	86.8%		1,057	86.7%	
Bifronto/temporal	306	13.2%		149	12.4%	
Pulse width at first ECT (ms)			678			141
0.25-0.49	437	26.6%		182	17.1%	
0.50	970	59.1%		736	69.0%	
0.51-1.20	235	14.3%		148	13.9%	
Charge at first ECT (mC)	307	226-404	671	307	230-409	141

Abbreviations: ECT: Electroconvulsive therapy; CGI-I: Clinical Global Impressions-Improvement; MADRS-S: Self-rated Montgomery-Åsberg Depression Rating Scale. IQR: interquartile range

[a] Data are from participants' first treatment series with the respective outcome.1,052 participants are included in both the MADRS-S and the CGI-I sample.


A. CGI−I
Polygenic risk score
MDD
BD
SCZ
$R^2 = 0.4\%$
$R^2 = 0.6\%$
$R^2 = 0.5\%$
$R^2 = 0.8\%$
$R^2 = 0.1\%$
$R^2 = 0.0\%$
0.66
0.80
1.00
1.25
1.50
Odds Ratio (95% Confidence Interval)
B. MADRS−S RESPONSE
Polygenic risk score
MDD
BD
SCZ
$R^2 = 0.8\%$
$R^2 = 0.8\%$
$R^2 = 0.4\%$
$R^2 = 0.5\%$
$R^2 = 0.1\%$
$R^2 = 0.0\%$
0.66
0.80
1.00
1.25
1.50
Odds Ratio (95% Confidence Interval)
C. MADRS−S REMISSION
Polygenic risk score
MDD
BD
SCZ
$R^2 = 1.0\%$
$R^2 = 0.9\%$
$R^2 = 0.6\%$
$R^2 = 0.5\%$
$R^2 = 0.6\%$
$R^2 = 0.6\%$
0.66
0.80
1.00
1.25
1.50
Odds Ratio (95% Confidence Interval)
Indication
All patients
Narrow (unipolar depression)


A. PRS−MDD QUINTILES (Reference = 1st quintile)
PRS−MDD quintile
2
3
4
5
0.50
0.66
0.80
1.00
1.25
1.50
2.00
Odds Ratio (95% Confidence Interval)
B. PRS−BD QUINTILES (Reference = 1st quintile)
PRS−BD quintile
2
3
4
5
0.50
0.66
0.80
1.00
1.25
1.50
2.00
Odds Ratio (95% Confidence Interval)
C. PRS−SCZ QUINTILES (Reference = 1st quintile)
PRS−SCZ quintile
2
3
4
5
0.50
0.66
0.80
1.00
1.25
1.50
2.00
Odds Ratio (95% Confidence Interval)
Indication
All patients
Narrow (unipolar depression)