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Association Between Polygenic Risk Scores and Outcome of ECT

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Abstract

Objective: Identifying biomarkers associated with response to electroconvulsive therapy (ECT) may aid clinical decisions. The authors examined whether greater polygenic liabilities for major depressive disorder, bipolar disorder, and schizophrenia 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), who had a registered treatment outcome, and whose polygenic risk scores (PRSs) could be calculated. Ordinal logistic regression was used to estimate the effect of PRS on Clinical Global Impressions improvement scale (CGI-I) score after each ECT series.

Results: Greater PRS for major depressive disorder was significantly associated with less improvement on the CGI-I (odds ratio per standard deviation, 0.89, 95% CI=0.82, 0.96; R^2=0.004), and greater PRS for bipolar disorder was associated with greater improvement on the CGI-I (odds ratio per standard deviation, 1.14, 95% CI=1.05, 1.23; R^2=0.005) after ECT. PRS for schizophrenia was not associated with improvement. In an overlapping sample (N=1,207) with data on response and remission derived from the self-rated version of the Montgomery-Åsberg Depression Rating Scale, results were similar except that schizophrenia PRS was also associated with remission.

Conclusions: Improvement after ECT is associated with polygenic liability for major depressive disorder and bipolar disorder, 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.

Electroconvulsive therapy (ECT) is an effective treatment for major depressive episodes, 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 because of definitional variation (2, 8). Notably, ECT is similarly effective in unipolar and bipolar depression (9, 10). Bipolar disorder has a higher estimated heritability than major depressive disorder (11), but we recently showed (12) that the single-nucleotide polymorphism (SNP)–based heritability of ECT-treated depression is considerably higher (29%–34%) than that of mild to moderate depression (6.5%–8.0%), suggesting that more heritable “biological” depression is more likely to be treated with ECT.

Polygenic risk scores (PRSs) are quantitative measures of the polygenic liability for complex traits, calculated from the summary statistics of genome-wide association studies (GWASs) (13). Although PRSs 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 patients experiencing major depressive episodes found that greater PRS for schizophrenia 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 major depressive episode also suggests that improvement after ECT might be associated with greater polygenic liability for major depressive disorder and bipolar disorder, the two disorders for which ECT is recommended as a treatment for a severe major depressive episode (20).

Our aim in the present study was to investigate whether therapeutic response following ECT for a major depressive episode is associated with PRSs for major depressive disorder, bipolar disorder, and schizophrenia. To this end, we analyzed a large cohort of Swedish patients who had received ECT for a major depressive episode.

METHODS

Study Population

The study population was derived from the Predictors for ECT (PREFECT) study, conducted in Sweden (12). Recruitment occurred between 2013 and 2017. Study participants had received at least one acute ECT series that was 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 a major depressive episode. Blood samples were stored at −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 a major depressive episode. 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 broadly defined group included participants with a major depressive episode occurring in the context of any one of the following: 1) a unipolar depressive disorder (ICD-10 codes F32–F33, F41.2, F53.0), 2) bipolar disorder (code F31), 3) another severe mood disorder with a pretreatment score≥20 on the self-rated Montgomery-Åsberg Depression Rating Scale (MADRS-S) (mixed anxiety and depressive disorder, code F41.2; schizoaffective disorder,

code F25.9; or mood disorder not otherwise specified, code F34.9), or4) major depressive episode as indicated by free text, or by a pretreatment MADRS-S score ≥20 if the specific indication for treatment was missing. The narrowly defined group consisted of the subset of participants who received ECT for a major depressive episode in the context of a unipolar depressive episode only. Psychotic features were considered present if the indication for ECT was coded with any of 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 improvement (CGI-I) score (22), rated immediately after the ECT series. We chose the CGI-I because it had the lowest proportion of missing information. CGI-I scores were available for the first registered treatment series of 92.8% of participants (N=2,154). CGI-I score, which ranges from 1 (very much improved) to 7 (very much worse), was treated as an ordinal variable. Secondary outcome measures were response and remission according to the MADRS-S (23). Both pre- and posttreatment MADRS-S scores were available for 52.0% of the sample (N=1,207), of which 79.2% (N=956) provided MADRS-S ratings at their first registered treatment series. The MADRS-S includes nine items rated from 0 to 6 (maximum score=54), which correspond to the items in the observer-rated MADRS except “apparent sadness.” Response was defined as a reduction ≥50% in MADRS-S score from pre- to posttreatment assessment. Remission was defined as a posttreatment MADRS-S score ≤10.

A subset of 1,052 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 $\rho=0.48$, $p<0.001$) and MADRS-S remission (Spearman’s $\rho=0.42$, $p<0.001$).

ECT Procedure

ECT was administered using bidirectional, constant-current, brief-pulse devices from Mecta (Mecta Corp., Lake Oswego, Ore.) or Thymatron (Somatics, Inc., Lake Buff, Ill.). 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 0.25–0.49 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 and imputation have been described in detail elsewhere (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 quality control was applied using the PGC RICOPILI pipeline (24). All potential samples were included in quality control, but the final association analysis was performed on the phenotyped subsets outlined above that passed quality control. 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 three standard deviations from the European reference population mean for principal components 1 or 2 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 that passed quality control 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

PRSs were calculated for major depression and bipolar disorder using discovery GWAS summary statistics from the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/download-results/) based on large GWASs for each phenotype (major depressive disorder: “mdd2019edinborough” [27]; bipolar disorder: “bip2019” [28]; schizophrenia: “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.

PRSs 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 1,000 Genomes Project European samples for the reference (phase 3 v5) (25). PRSs were calculated using PLINK, version 1.9 (30). PRSs were coded as risk increasing and standardized to a mean of 0 and a standard deviation of 1 for interpretability. To reduce the number of comparisons, we used the PRSs calculated at a p threshold of ≤0.05 as exposures in our main analyses, in alignment with previous research (17). Table S1 in the online supplement 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 (and percent) or median (and interquartile range). Our primary analyses investigated the associations of PRSs for major depression, bipolar disorder, and schizophrenia with CGI-I score. 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 >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 PRS values 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 odds ratios with 95% confidence intervals. For all analyses, we calculated the proportion of variance explained by each PRS as the difference between the Nagelkerke 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 major depressive episode. Second, we repeated the analyses using PRS calculated on the basis of alternative p-value inclusion thresholds (≤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 placement) at first or last ECT, and for participants with versus 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 scores because of the analyses of three PRSs. 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, N.Y.) for data management, and STATA, version 16 (Stata-Corp, College Station, Tex.) for statistical analyses. Figures were produced in R, version 4.0.5 (R Foundation for Statistical Computing, Vienna) using *ggplot2*, version 3.3.3 (31).

RESULTS

Sample Characteristics

We included 2,320 individuals of European genetic ancestry in the primary outcome analysis (CGI-I) (Table 1). The median age was 51 years, 62.8% were women, and 77.1% had a major depressive episode in the context of major depression (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 presented in Figure S1 in the online supplement.

Primary Outcome

Inheritance of a greater burden of common, risk-increasing genetic variants associated with major depression (major depression PRS) was significantly and negatively associated with improvement after ECT (CGI-I, odds ratio for improvement, 0.89 per SD, 95% CI=0.82, 0.96, p=0.002, Nagelkerke R^2=0.004) (Figure 1A; see also Table S2 in the online supplement). Participants in the highest quintile of major depression PRS had 31% lower odds of improvement compared to those with the lowest burden (quintile 5 vs. 1, odds ratio=0.69, 95% CI=0.54, 0.87, p=0.002) (Figure 2A; see also Table S3 in the online supplement).

Higher bipolar disorder PRS was significantly and positively associated with improvement after ECT (odds ratio per SD,1.14,95%CI=1.05,1.23,p=0.003,Nagelkerke R^2=0.005). Participants in the highest quintile for genetic burden of bipolar disorder had 44% higher odds of improvement after ECT than those with the lowest burden (quintile 5 vs. 1, odds ratio=1.44, 95% CI=1.13, 1.84, p=0.003) (Figure 2B; see also Table S3 in the online supplement). Schizophrenia PRS was not associated with improvement after ECT (odds ratio 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 major depression PRS and bipolar disorder quintiles, which therefore should be interpreted with caution (see Table S3 in the online supplement). In a post hoc analysis, we also found that a PRS (at p≤0.05) of percentage improvement on antidepressants (32) was not associated with improvement following ECT (see Table S4 in the online supplement).

Secondary Outcomes

For the MADRS-S analysis, 1,207 participants were eligible. Participant characteristics were similar to those of the CGI-I sample:64% were female and 67.5% belonged to the narrowly defined group (a major depressive episode in the context of major depression) (Table 1). After ECT, 60.1% (N=725) met the criterion for response (Table 1). Similar to the primary analysis, higher major depression PRS was associated with lower odds of response (odds ratioper SD, 0.85, 95% CI=0.76, 0.96, p=0.008, Nagelkerke R^2=0.008) (Figure 1B; see also Table S2 in the online supplement), while bipolar disorder PRS was associated with higher odds of response (odds ratio per SD, 1.13, 95% CI=1.00, 1.27, p=0.044, Nagelkerke R^2=0.004). Schizophrenia PRS was not associated with response (odds ratio 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 major depression PRS was associated with lower odds of remission (odds ratio per SD, 0.83, 95% CI=0.73, 0.94, Nagelkerke R^2=0.01, p=0.002) (Figure 1C; see also Table S2 in the online supplement), while bipolar disorder PRS was associated with higher odds of remission (odds ratio per SD, 1.15, 95% CI=1.02, 1.29, p=0.023, Nagelkerke R^2=0.006), as was schizophrenia PRS (odds ratio per SD, 1.16, 95% CI=1.02, 1.31, p=0.020, Nagelkerke R^2=0.006).

Sensitivity Analyses

We repeated the primary analyses restricting the sample to participants with narrowly defined major depressive episode in the context of major depression and obtained similar results (Figures 1 and 2; see also Tables S2 and S3 in the online supplement). The results were not sensitive to the choice of p-value threshold (see Figure S1 in the online supplement). Results were similar to those of the primary analysis in participants with unilateral electrode placement, but in the limited subsample treated with bilateral electrode placement (N=306), only major depression PRS was associated with improvement (see Table S5 in the online supplement). Among participants without psychotic features, results were similar to those of the main analysis (see Table S6 in the online supplement). No significant effect of any PRS was observed among participants with psychotic features (N=348), although point estimates were similar to those of the primary analysis.

DISCUSSION

We investigated whether improvement after ECT was associated with polygenic liability for major depression, bipolar disorder, and schizophrenia in a cohort of 2,320 patients with a major depressive episode. We found that higher polygenic liability for major depression was associated with lower chance of improvement after ECT, whereas higher polygenic liability for bipolar disorder was associated with higher Chance of improvement. In our primary analysis, we could not replicate the relatively strong association between increasing schizophrenia PRS and more improvement reported from a previous smaller study (19), although we did find that schizophrenia PRS was positively associated with remission according to MADRS-S score. 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 PRSs and therapeutics for mood disorders. Major depression PRS and schizophrenia PRS have been associated with lower likelihood of lithium response in patients with bipolar disorder (14, 15), while bipolar disorder PRS had no such association (18). No robust associations have been found with PRSs for psychiatric disorders and response to antidepressants (33–35); nominal associations of major depression PRS with less improvement on citalopram/escitalopram (34) or esketamine in treatment-resistant major depression (35) did not survive correction for multiple testing. Major depression PRS was not associated with outcome after cognitive-behavioral therapy for major depressive episode (17).

It is noteworthy that higher major depression PRS has been associated with poorer response to antidepressant treatments rather than the opposite. Higher major depression PRS has been related to more severe major depression (36), which in turn is believed to predict response to ECT (6, 8). But the measures of depression severity that have been associated with higher major depression PRS—early age at onset, higher symptom count, and a chronic/unremitting course of illness (36)—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).

In contradistinction to major depression PRS, we found that higher polygenic liability for bipolar disorder was associated with better response to ECT. The discrepancy between major depression PRS and bipolar disorder PRS 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 bipolar disorder PRS in patients with a severe major depressive episode treated with ECT than in patients with more moderate depression treated with Internet-based cognitive-behavioral therapy (12). Higher bipolar disorder PRS might thus reflect a genetic liability to develop not only bipolar disorder but also more severe depression. Our findings indicate that high polygenic liability for bipolar disorder may also

be associated with response to biological treatments, including ECT. Further research is needed to confirm this.

The effect sizes of PRSs in this study were small, which echoes other genetic studies of response to psychiatric treatments (14–16). Although effect sizes may increase with larger genomic studies (37), the power of PRS to explain treatment effects may be limited in cohorts with similar phenotypes and relatively small variations in treatment outcome. Also, the genetic correlation between major depression and bipolar disorder seems to be due to pleiotropic genetic variants, meaning that genetic risk for bipolar disorder cannot be used to delineate major depression subgroups (38). Thus, PRSs of bipolar disorder and major depression 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 may 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 (39).

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 (CGI-I) and secondary (MADRS-S) outcome measures. Sensitivity analyses provided further convergent evidence. Limitations of the study include, first, that data were collected in routine clinical practice, limiting quality supervision. This probably adds noise compared with controlled studies. Second, the MADRS-S is self-rated while the 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 poor mental states that precluded the completing of a self-rated instrument, and it 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 nonresponse to antidepressant medication (10). It remains to be examined to what extent the association between, for example, PRS for major depression and treatment outcome is independent of these variables. Last, given that our sample size was <4,000, the study was powered neither for a GWAS of ECT outcomes nor for computing heritability estimates for the studied outcomes (40).

In summary, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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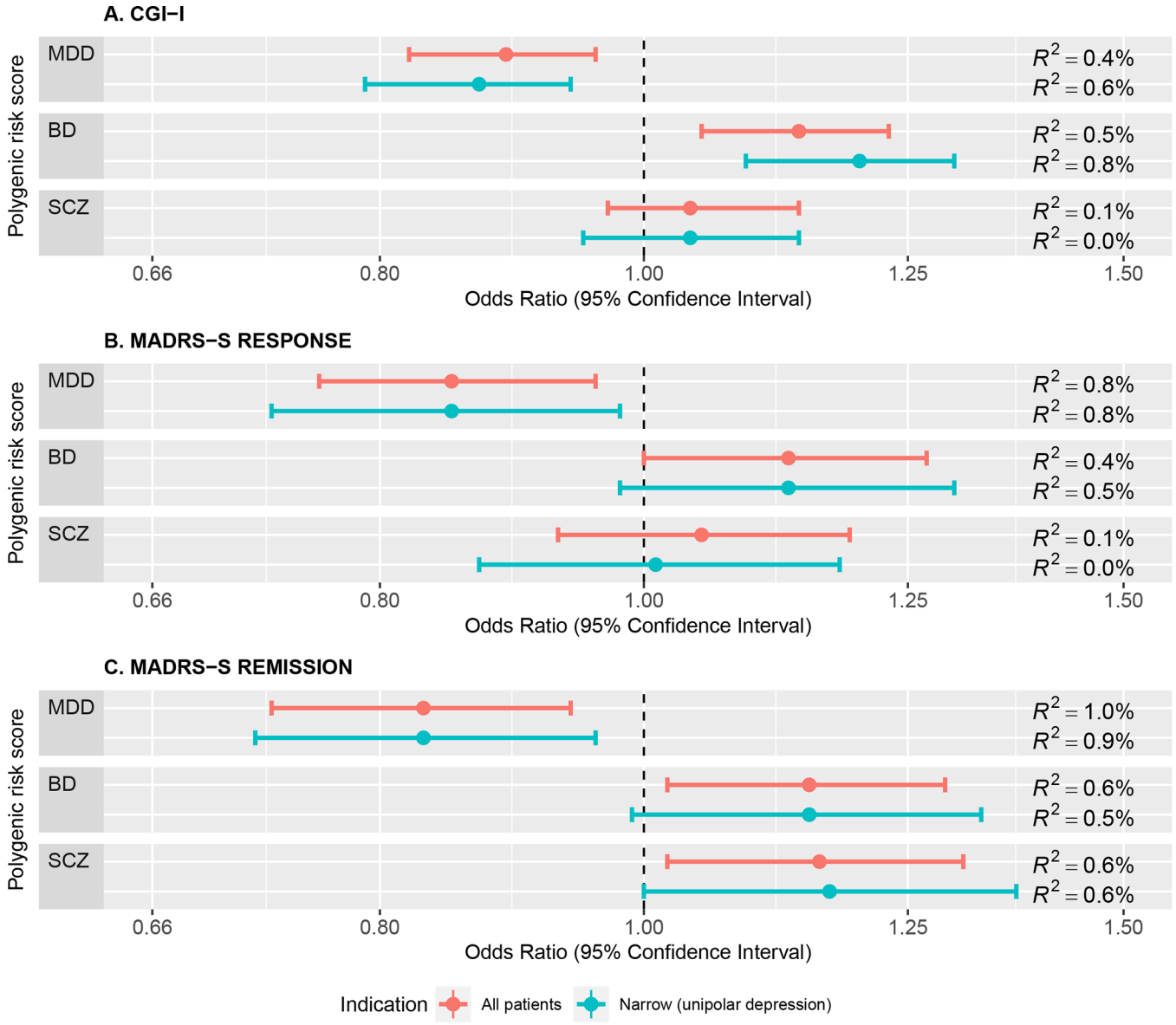

FIGURE 1. Association between polygenic risk scores (PRSs) and measures of improvement after ECT[a]

[a] The figure shows the associations between PRSs for major depression, bipolar disorder, and schizophrenia and outcomes of ECT among all participants (main analysis) and among only those with unipolar depression (sensitivity analysis). Odds ratios are per standard deviation of increasing PRS, and an odds ratio >1 indicates higher odds of favorable outcome. Error bars indicate 95% confidence intervals. The x-axis is logarithmic. Panel A shows associations with the primary outcome, score on the Clinical Global Impressions improvement scale (CGI-I) (all patients, N=2,320; narrowly defined group, N=1,789), estimated from an ordinal logistic regression model adjusted for the first five genetic ancestry principal components. Panels B and C show associations with response and remission on the self-rated Montgomery-Åsberg Depression Rating Scale (MADRS-S) (all patients, N=1,207; narrowly defined group, N=815), estimated from binary

logistic regression models adjusted for MADRS-S before ECT and the first five genetic ancestry principal components. BD=bipolar disorder; MDD=major depressive disorder; SCZ=schizophrenia.

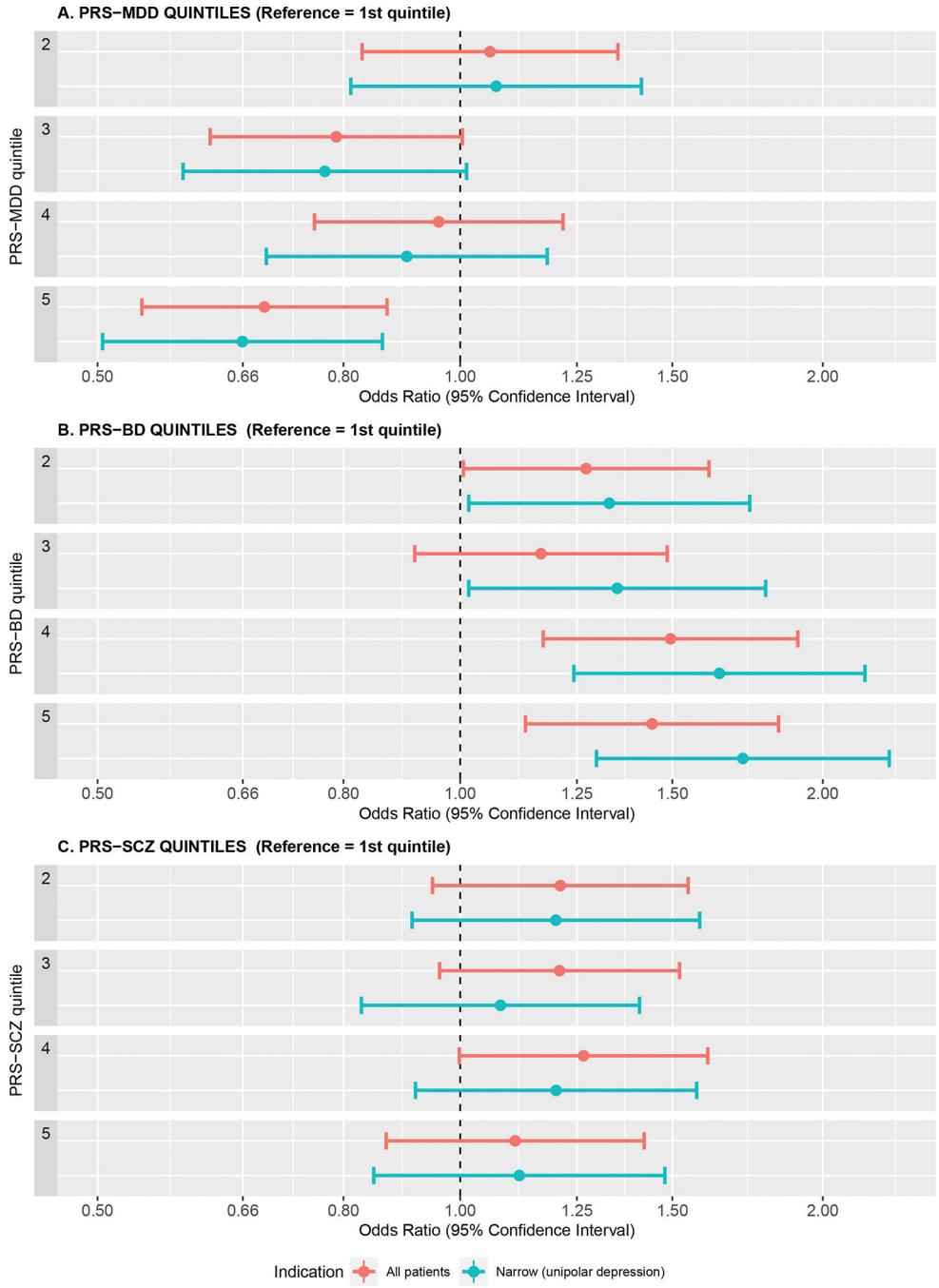

FIGURE 2. Associations between quintiles of polygenic risk scores (PRSs) and CGI improvement after ECT[a]

[a]The figure shows the odds of more improvement after ECT according to Clinical Global Impressions improvement scale (CGI-I) score for each quintile of PRS relative to the 1st quintile (all patients, N=2,320; narrowly defined group, N=1,789), estimated from ordinal logistic regression models adjusted for the first five genetic ancestry principal components. Error bars indicate 95% confidence intervals. The x-axis is logarithmic.

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%	
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	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 ECT			15			131
Unilateral	2,109	91.5%		998	92.8%	
Bitemporal / bifrontal	196	8.5%		78	7.2%	
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.