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Schizophrenia Polygenic Risk Score as a Predictor of Antipsychotic Efficacy in First Episode Psychosis

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Abstract

Objective: Pharmacogenomic studies of antipsychotics have typically examined effects of individual polymorphisms; by contrast, polygenic risk scores (PRS) derived from genome-wide association studies (GWAS) can quantify the influence of thousands of common alleles of small effect in a single measure. We examined whether PRS for schizophrenia are predictive of antipsychotic efficacy in four independent cohorts of patients with first-episode psychosis (total n=510).

Method: All subjects received initial treatment with antipsychotic medication for first-episode psychosis, and all were genotyped on standard SNP arrays imputed to the 1000 Genomes reference panel. PRS was computed based on the results of the large-scale schizophrenia GWAS reported by the Psychiatric Genomics Consortium. Symptoms were measured by total symptom rating scales at baseline and week 12 or at the last follow-up visit before drop-out.

Results: In the discovery cohort, higher PRS significantly predicted higher symptom scores at 12-week follow-up (controlling for baseline symptoms, sex, age, and ethnicity). The PRS

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threshold of P_T<0.01 gave the strongest result in the discovery cohort, and was used to replicate the findings in the other three cohorts. Higher PRS significantly predicted greater post-treatment symptoms in the combined replication analysis (p=.0095), and was individually significant in two of the three replication cohorts. Across the four cohorts, PRS was significantly predictive of adjusted 12-week symptom scores (pooled partial r=0.18, p=0.002, 3.24% of variance explained). Patients with low PRS were more likely to be treatment responders than those with high PRS (OR=1.91 in Caucasian samples, p<0.01).

Conclusion: Patients with higher PRS for schizophrenia tended to have less improvement with antipsychotic drug treatment. PRS burden may have potential utility as a prognostic biomarker.

Introduction

Genetic susceptibility to schizophrenia is highly polygenic, including many associated loci of small effect(1, 2). While individual risk alleles may convey an odds ratio of 1.1 or lower, the combination of all such effects across the genome holds substantial explanatory power. For example, any individual can be characterized by a polygenic risk score (PRS), representing the total number of risk alleles he or she carries, weighted by the odds ratio associated with each allele as derived from previous genome-wide association study (GWAS) findings(3, 4). While a high PRS for schizophrenia is not deterministic, PRS derived from the Psychiatric Genomics Consortium(1) accounts for approximately 7% of variation in risk for schizophrenia (as measured on the liability scale(5), with about half of that variance accounted for by the top (genome-wide significant) loci. Additionally, individuals scoring in the top decile are ~15 times more likely to manifest the illness compared to those in the bottom decile(1).

Given the explanatory power of PRS for susceptibility to schizophrenia, it is reasonable to ask whether these scores can be informative regarding clinical heterogeneity within the disorder(2). For example, while antipsychotic drugs are the mainstay therapy for schizophrenia(6, 7), up to 30-40% of patients do not respond to antipsychotic treatment(8), and many patients discontinue their medications due to lack of efficacy(9). There is currently a paucity of clinically informative biomarkers, and pharmacogenomics is one approach to identifying predictors of treatment response(10). To date, candidate-gene studies and a small number of genome-wide association studies (GWAS) have had limited success in identifying genetic variants replicably associated with antipsychotic treatment response. So far, only two variants (at the *DRD2* gene and the *COMT* gene) have demonstrated consistent effects across multiple cohorts as demonstrated by meta-analysis(11, 12). Although promising, their effect sizes are relatively small (OR's = 1.54 and 1.37, respectively) and predictive power is limited(13).

Given previous findings suggesting that a family history of schizophrenia may be associated with poor clinical response(14, 15), patients with higher genetic burden of schizophrenia may have poorer clinical outcomes. Compared to candidate gene approaches, PRS methods may better capture the full genomic underpinnings of illness and improve clinical prediction, as has been recently demonstrated in prostate cancer, in which higher PRS was associated with more aggressive illness(16). One recent schizophrenia study utilized clinically assigned

clozapine therapy as a proxy for treatment resistance (by comparing clozapine-treated patients to those who have never been prescribed clozapine) and found that PRS was significantly higher in clozapine patients than in non-clozapine patients(17), although another study failed to replicate the finding (18). However, both were cross-sectional studies that can be affected by ascertainment bias and inaccuracies of classification; for example, a similar cross-sectional study providing evidence for a pharmacogenetic role for the *BDNF* Val66Met variant(19) was not supported by subsequent longitudinal studies conducted in the context of clinical trials(20). Furthermore, PRS may have additional advantages in clinical prediction because it is a continuous variable that can have different cutoffs that maximize predictive power, whereas the candidate gene approach can compare only carriers to non-carriers. Moreover, its predictive power will increase as the discovery sample gets larger.

In the present study, we aimed to investigate whether PRS based on the large-scale GWAS conducted by the Psychiatric Genomics Consortium (PGC)(1) is predictive of antipsychotic efficacy in patients with first-episode non-affective psychosis. There are several advantages of studying first-episode psychosis, such as minimal or no prior drug exposure, increased effect size of genotype-phenotype association(21), and representation of the whole patient population compared to chronic patient samples which may be subject to ascertainment biases(22). While one prior study examined PRS in relation to clinical response to lurasidone in patients with chronic schizophrenia(23), this is the first study, to our knowledge, to longitudinally examine treatment response in first episode patients undergoing initial treatment with antipsychotics.

Methods

Participants

The discovery cohort consists of 77 patients from the Zucker Hillside Hospital First Episode schizophrenia trial (ZHH-FE)(24). They were treated with either risperidone or olanzapine for 16 weeks and psychotic symptoms were assessed by the Schedule for Affective Disorders and Schizophrenia Change Version with psychosis and disorganization items (SADS-C+PD) at baseline and weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, and 16. To compute a total symptoms score, selected items from the SADS-C+PD were converted to corresponding items in the Brief Psychiatric Rating Scale (BPRS)(25) and a total score of the imputed BPRS was calculated(26). Last-observation-carry-forward (LOCF) method was used for missing data and the change score from baseline to week 12 was computed as the main phenotype of total symptom reduction after treatment. Week 12 data was chosen to be consistent with other cohorts. The patients were from several different continental ancestries including European, African, Asian, and mixed ancestry.

Three additional cohorts were used for replication of the findings from the discovery sample. 1) The European First Episode Schizophrenia Trial (EUFEST) cohort: patients were randomized to one of five antipsychotics: olanzapine, quetiapine, ziprasidone, amisulpride, and haloperidol, and treated for up to 12 months(27). Symptoms were assessed with the Positive and Negative Symptoms Scale (PANSS)(28). Genomic data was available for 150 patients. All 141 European-ancestry patients were included in the present study and 9 patients from other racial groups were excluded to make the sample more homogeneous.

LOCF method was used for missing data at 3 months. 2) The Programa Asistencial Fases Iniciales de Psicosis (PAFIP) de Cantabria, Spain (29, 30). Patients were treated with aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone for 12 weeks. Data were available for 192 patients with DNA and BPRS ratings at baseline and 12 weeks. All subjects were of European ancestry. 3) The third cohort consists of 100 patients from the clinical trial as part of the Center for Intervention Development and Applied Research at ZHH (CIDAR) and they were treated with either risperidone or aripiprazole for 12 weeks, and symptoms were assessed by the BPRS(31). Again, LOCF method was used for missing data. Like the ZHH-FE sample, the CIDAR patients came from various ancestry groups. Table 1 shows the demographic data for the four cohorts.

Genotyping

DNA was extracted from peripheral lymphocytes and genotyping was performed using the Illumina Omni-1 Quad (ZHH-FE and EUFEST samples) or Illumina Infinium HumanOmniExpressExome platform (CIDAR and PAFIP samples). Standard quality control procedures were performed to exclude SNPs with minor allele frequency (MAF) <2%, genotyping failure >5%, Hardy-Weinberg equilibrium $p<10^{-6}$, mismatch between recorded and genotyped sex, as well as related individuals (the relative with the lower call rate was dropped). SNP imputation was conducted with IMPUTE2(32) against the full 1000 Genomes phase 3 reference panel(33). The imputed SNPs underwent another round of quality control and SNPs with missing data >5% and imputation information score <0.8 were excluded. The discovery cohort ended up with 6,143,400 high quality SNPs. The EUFEST, PAFIP, and CIDAR samples had 6,863,830, 7,302,869, and 7,302,858 SNPs, respectively, after quality control. Principle component analysis was conducted in each cohort and the top 3 principal component scores were saved for further analysis. All genomic data analysis was performed using the SVS software, version 8.7.0 (Golden Helix, Inc., Bozeman, MT, USA).

Polygenic Risk Scores (PRS)

PRS based on the PGC schizophrenia GWAS(1) represents a measure of genetic liability to schizophrenia. The higher an individual's PRS, the higher his/her risk of schizophrenia. PRS was calculated for each participant in the sample as the weighted sum of the risk allele they carried, based on the summary statistics (effect alleles and odds ratios) derived from the clumped PGC GWAS results, which consists of 102,636 SNPs. The clumped PGC GWAS summary statistics file was downloaded from the LD Hub at the Broad Institute (available at http://ldsc.broadinstitute.org/ldhub/). The clumping parameters are as following: a SNP will be clumped to a more significant SNP with LD ($r^2 \geq 0.10$) within a 500kb window, with the MHC region represented by a single SNP. The calculation was carried out in the PRSice software(4) for the four cohorts separately. SNPs were selected to be included in the PRS calculation based on their p values in the original PGC GWAS. For the discovery cohort (ZHH-FE), the PRS was calculated at several p value thresholds (P_T) based on the original PGC GWAS, in order to explore which one would maximize the signal of PRS-phenotype association. Specifically, P_T's $\leq 5\times10^{-8}$, 0.001, 0.01, 0.05, 0.10, 0.20, and 0.50 were applied to compute seven sets of PRS for the discovery cohort. The P_T with maximum prediction power for the outcome variable in the discovery cohort was then used for computing the

PRS for the three replication cohorts. PRS data were approximately normally distributed, and were converted into z scores for easy interpretation.

Statistical Analysis

The primary phenotype was antipsychotic drug efficacy, defined by symptom reduction from baseline to 12 weeks or 3 months. Symptoms were measured using the total score of BPRS items (derived from the SADS-C+PD) for the ZHH-FE cohort, total BPRS scores for the PAFIP and CIDAR samples, or the total PANSS score for the EUFEST sample. The 12-week (or 3-month) scores, adjusted for the baseline scores, age, and sex, served as the primary dependent variable in a hierarchical linear regression; PRS was the predictor variable. The endpoint score adjusted for baseline value in a regression analysis is functionally equivalent to the simple change score from baseline to endpoint, but is statistically more powerful. Genomic principal component scores were also covaried to control for population stratification for the ZHH-FE and CIDAR cohorts because they consisted of subjects of various ancestries, while the EUFEST and PAFIP cohorts were entirely of European descent. Meta-analysis was performed to combine the effect sizes (partial correlation coefficients) from the three replication cohorts, as well as all four cohorts combined, because each cohort had a relatively small sample size. While it is not uncommon for replication tests to be reported with one-tailed p-values, we report two-tailed tests for all analyses for purposes of clarity and to remain conservative in reporting significant results. All statistical analyses were performed using SPSS version 24 (IBM, Armonk, NY, USA).

Results

Discovery Cohort

Among the 77 patients in the ZHH-FE cohort, higher PRS at the thresholds of $P_T<0.01$, 0.05, 0.10, 0.20, and 0.50 significantly predicted worse response to treatment (i.e., higher symptom scores at 12-week follow-up), explaining between 6.4% and 8.1% of the total variance in outcome (all p's<.05; Figure 1). PRS at the threshold $P_T < 5\times10^{-8}$ and $P_T < 0.001$ were not significant in predicting the symptom change scores (p=.54, p=.28, respectively). PRS at $P_T<0.01$ gave the strongest result in the discovery sample, and therefore was used to replicate the findings in the other three cohorts.

Replication Cohorts and Meta-analysis

Higher PRS (at $P_T<0.01$) significantly predicted worse outcome (i.e, higher symptoms at the 12-week or 3-month follow-up) across the three replication cohorts (pooled partial r = 0.15, p = 0.019). Moreover, this relationship was statistically significant in the EUFEST and PAFIP cohorts individually, explaining 3.5% and 3.7% of variance respectively (Table 2). Figure 2 shows the scatter plot and fitted regression line of PRS at $P_T<0.01$ on adjusted symptom scores at the 12-week follow-up. Importantly, these results were not simply a function of PRS-related differences in baseline symptoms; PRS was not significantly correlated with baseline total symptoms in any of the four cohorts (p=.23, p=.52, p=.15, p=.43, respectively). As an exploratory analysis, PRS at other p-value thresholds were also used to predict antipsychotic efficacy in the same regression model (see Supplemental Table S1).

Combining the four cohorts in a meta-analysis with a random effects model, PRS (at $P_T<0.01$) was significantly predictive of 12-week symptom scores (pooled partial correlation coefficient=0.18, p=0.002, total n = 510; Figure 3). Heterogeneity measures for the meta-analysis showed Q = 4.68, df=3, p=0.20, and I^2 = 36%, indicating relatively homogeneous findings. The overall results remained significant when only European ancestry individuals were included in the meta-analysis (pooled partial r = 0.19, p<0.001, total n=387).

To test the specificity of schizophrenia PRS predicting antipsychotic drug response, we repeated the same analysis using polygenic risk scores for type 2 diabetes based on the GWAS findings from the DIAGRAM (DIAbetes Genetics Replication And Meta-analysis) consortium(34), and polygenic risk scores for human height based on the GWAS findings from the GIANT consortium(35). Neither of these polygenic risk scores, at any P_T threshold, significantly predicted symptom change in any of the four cohorts (all p>.05; mean p=0.69, median p=0.74).

To rule out the potential confounding effects of early drop-out, we ran the analysis for completers only in the ZHH-FE, EUFEST, and CIDAR cohorts excluding subjects who dropped out prior to the end of the study. (The PAFIP analysis was already completers-only based on the original design of that trial). The results were essentially unchanged.

Clinical Implications

To explore clinical significance of this finding, response rate was calculated in each cohort with the definition of treatment response as 50% or more reduction in total symptoms scores (either BPRS or PANSS) from baseline to 12-week follow-up. Each cohort was divided into high versus low PRS groups with a median split. Combining the four cohorts, the response rate was 60.9% (154 out of 253) in the low PRS group, compared to 52.1% (134 out of 257) in the high PRS group, χ^2 = 3.95, df = 1, p = 0.047, odds ratio (OR) = 1.43. Because it is not possible to control for genomic principal components in this categorical analysis, we repeated the analysis for cohorts consisting of European ancestry only (i.e., EUFEST and PAFIP). Combining the two cohorts, the response rate in the low PRS group was 61.8% (102/165), while it was 45.8% (77/168) in the high PRS group (χ^2 = 8.56, df = 1, p = 0.0034, OR = 1.91). Supplemental Table 2 provides the response rate in each cohort, separated by Caucasians and non-Caucasians.

Discussion

In multiple cohorts of first-episode patients with non-affective psychosis, we found that schizophrenia polygenic risk scores were significantly predictive of antipsychotic drug efficacy, with higher PRS associated with poorer treatment response. These results suggest that polygenic burden may impact severity of illness, in addition to reflecting risk for developing psychosis. To the best of our knowledge, this is the first study predicting antipsychotic efficacy based on schizophrenia PRS examining patients undergoing initial treatment for a first episode of illness and utilizing multiple cohorts for replication of effects.

Only a few prior studies have examined the relationship of PRS to treatment response. Consistent with our findings, a cross-sectional study reported significantly higher PRS in

patients with treatment-resistant schizophrenia (as indexed by taking clozapine and who also had early, insidious onset and poor premorbid social function) as compared to patients who had never been prescribed clozapine.(17) However, in the same study, clozapine responders had higher schizophrenia polygene scores than non-responders to clozapine, suggesting that treatment with clozapine may be an important (and perhaps under-utilized) treatment option for patients with high PRS. A second cross-sectional study reported a similar trend, with clozapine initiation associated with elevated PRS(18). However, it should be noted that results fell just short of statistical significance (adjusted hazard ratio=1.23; 95% confidence interval=0.97-1.56), albeit with smaller sample size (n=105 clozapine patients) compared to the prior study (n=434 clozapine patients)(17). Notably, the association between PRS and clinical outcome was weaker (and nonsignificant) for more broadly defined treatment resistance based on chart history, indicating the importance of prospective studies(18). The only longitudinal study examining the relationship of PRS to treatment response demonstrated a paradoxical inverse relationship, such that higher scores were associated with greater reduction in symptoms after six weeks of treatment with lurasidone(23). It is possible that ascertainment criteria of this lurasidone clinical trial may have affected results, insofar as treatment-resistant patients were explicitly excluded, and patients with good clinical outcomes on standard treatments would not have enrolled in Phase III clinical trial of a novel antipsychotic.

Studies of patients in the first episode have the advantage of examining the full range of clinical trajectories of schizophrenia, before patients become lost to research due to either very good or very bad outcomes.(22) Only two reports have examined PRS in the context of first episode psychosis(36, 37). In contrast to the present study, both of these reports included patients with affective as well as non-affective psychosis, but results are largely consistent with the present findings. The first study revealed higher schizophrenia PRS in patients ultimately diagnosed with schizophrenia relative to those with affective psychoses(31). The second study, although longitudinal, did not directly report on treatment-related changes; nevertheless, higher PRS was significantly and positively correlated with PANSS total scores after one month of treatment(37).

Pharmacogenetic studies of antipsychotic drug response have typically focused on individual genes and SNPs in the candidate gene approach. Although a few genes have been reported to predict antipsychotic efficacy, such as *DRD2*(11, 38), *HTR2A*(39, 40), and genes in the glutamate system(41), most SNPs had small effect sizes, few have been convincingly replicated (10,11) and their clinical significance is questionable. Although dopamine D2 receptor antagonism is the common, and probably necessary, mechanism of action for antipsychotic drugs, these agents bind to many different receptors of various neurotransmitters(42), and it is very likely that some of these may involve in antipsychotic drug response(43). Perhaps more importantly, many of the drug effects may be from down-stream reactions within the dopamine signaling pathway. Therefore, the examination of multiple genes is important because this may help capture the potential down-stream effects from antipsychotic drugs. In addition, PRS represents the total genetic burden of liability to schizophrenia. Conceivably, higher genetic burden may implicate a broader range of etiopathophysiologic mechanisms, thereby rendering patients less responsive to drug treatment based primarily on a single mechanism of action (dopaminergic blockade). As

such, the PRS approach may be useful in both practical and theoretical sense in predicting clinical treatment response.

There are several limitations in the present study. PRS is a weighted sum of risk alleles an individual carries. Many of the SNPs included in PRS may not be relevant to antipsychotic drug response, and inclusion of these could dilute the signal. We observed that statistical association was generally significant using PRS thresholds of $P_T \geq 0.01$, suggesting that thousands of SNPs are required in order to saturate the relevant signal, while use of only SNPs attaining genome-wide significance in the PGC schizophrenia GWAS was insufficient to capture this variance. However, we currently do not have sufficient biological knowledge or statistical techniques to ascertain which SNPs are relevant and which are contributing noise. In addition, the four cohorts of patients were treated with various antipsychotic drugs which could increase the heterogeneity in outcomes, thereby decreasing our ability to detect significant signals. In the future, a very large sample of first-episode patients undergoing a single drug treatment would be required to discover which genetic variants are involved in antipsychotic drug response. Finally, PRS was not predictive of antipsychotic treatment response in the CIDAR cohort. If the true effect size is most accurately reflected in the meta-analytic result (r=.18), then a sample with n=100 (such as CIDAR) would only have power of .42 to detect a significant effect. Therefore, the failure to replicate in the CIDAR cohort was most likely due to chance variation, possibly exacerbated by the multi-ethnic nature of the sample. Notably, the overall pooled effect size is within the 95% confidence interval of the effect size in the CIDAR cohort, so this sample is not truly an outlier. At the same time, the effect size observed in the initial discovery cohort was substantially larger than the remaining cohorts, perhaps reflective of the winner's curse. Given these variable results, it is noteworthy that the meta-analytic effect size (3.24%) is comparable to the effect sizes of the two largest (and most homogeneous studies (3.5-3.7%).

Future studies with larger samples may also result in the ability to identify a PRS cutoff with sufficient explanatory power to attain clinical utility. In the present study, we observed an odds ratio of nearly 2 for dichotomized treatment response in patients with low PRS compared to patients with high PRS. While this effect size is insufficient to guide clinical decision making, a recent large-scale study of PRS in bipolar disorder demonstrates how modest effect sizes may still allow clinical utility at the extremes(44). With a sample size of 2586 patients, the International Consortium on Lithium Genetics (ConLi$^+$Gen) was able to divide the cohort into deciles on the basis of PRS, whereas the present study was limited to a median split due to relatively smaller sample size. In the ConLi$^+$Gen study, bipolar patients in the lowest decile of schizophrenia PRS had a nearly 3.5-fold better response rate to lithium, compared to patients in the highest decile of PRS. Notably, a median split of the ConLi$^+$Gen data would have provided an odds ratio of only 1.68, which is weaker than that observed in the present study. Given the linear relationships observed in the present study (Figure 2), it is reasonable to hypothesize that a larger sample size could provide an upper cutoff with strong prognostic ability. In this regard, PRS may ultimately be a more flexible and powerful biomarker than individual SNPs, which only permit 3 genotypic classifications. However, if greater schizophrenia polygenic burden is associated with poorer response to all conventional treatments, enhanced utilization of clozapine and/or novel therapeutic approaches(45) will be even more urgently needed for this subpopulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosure

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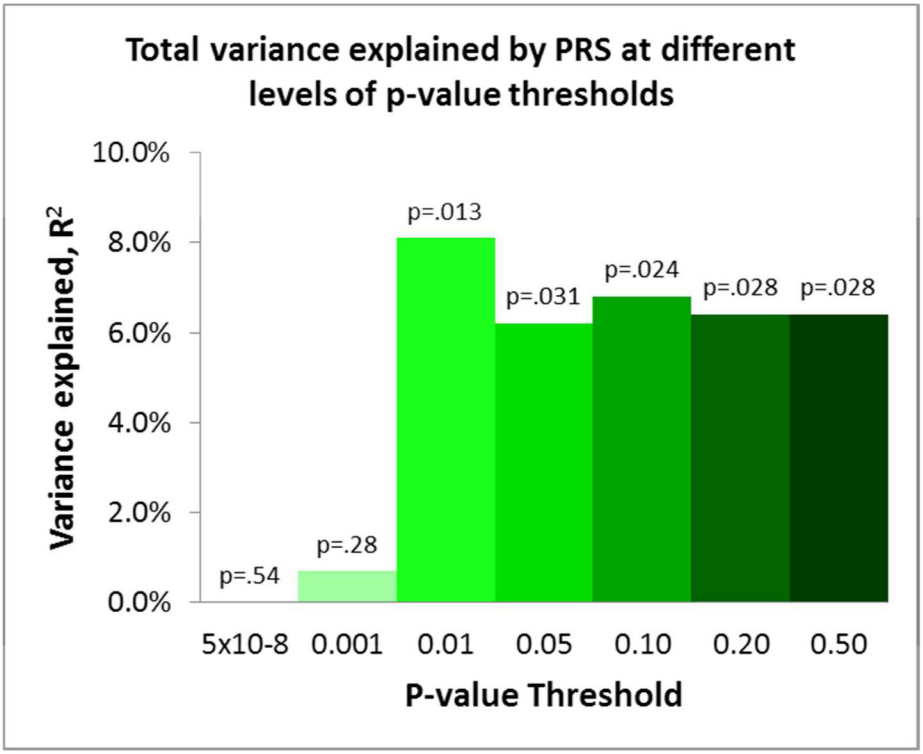
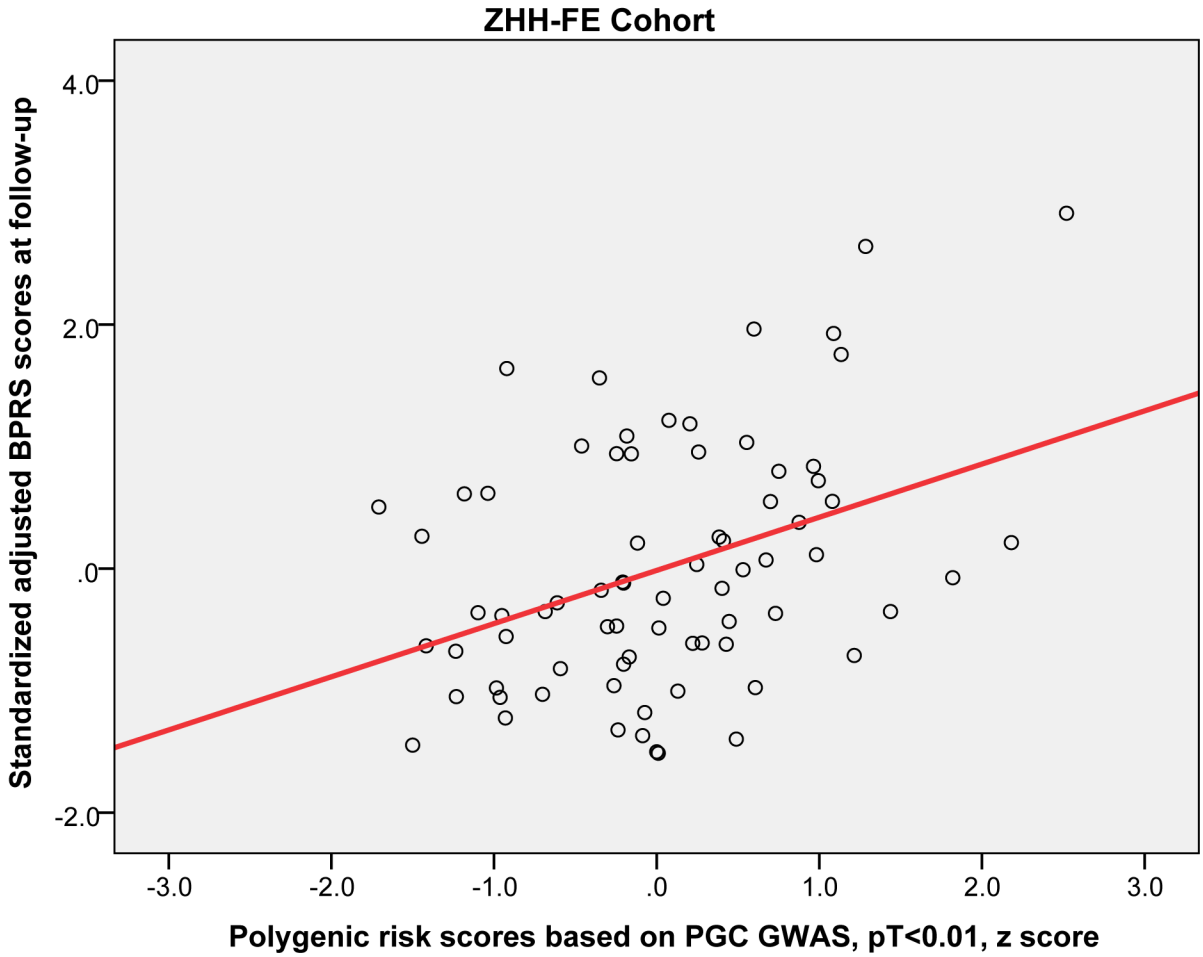
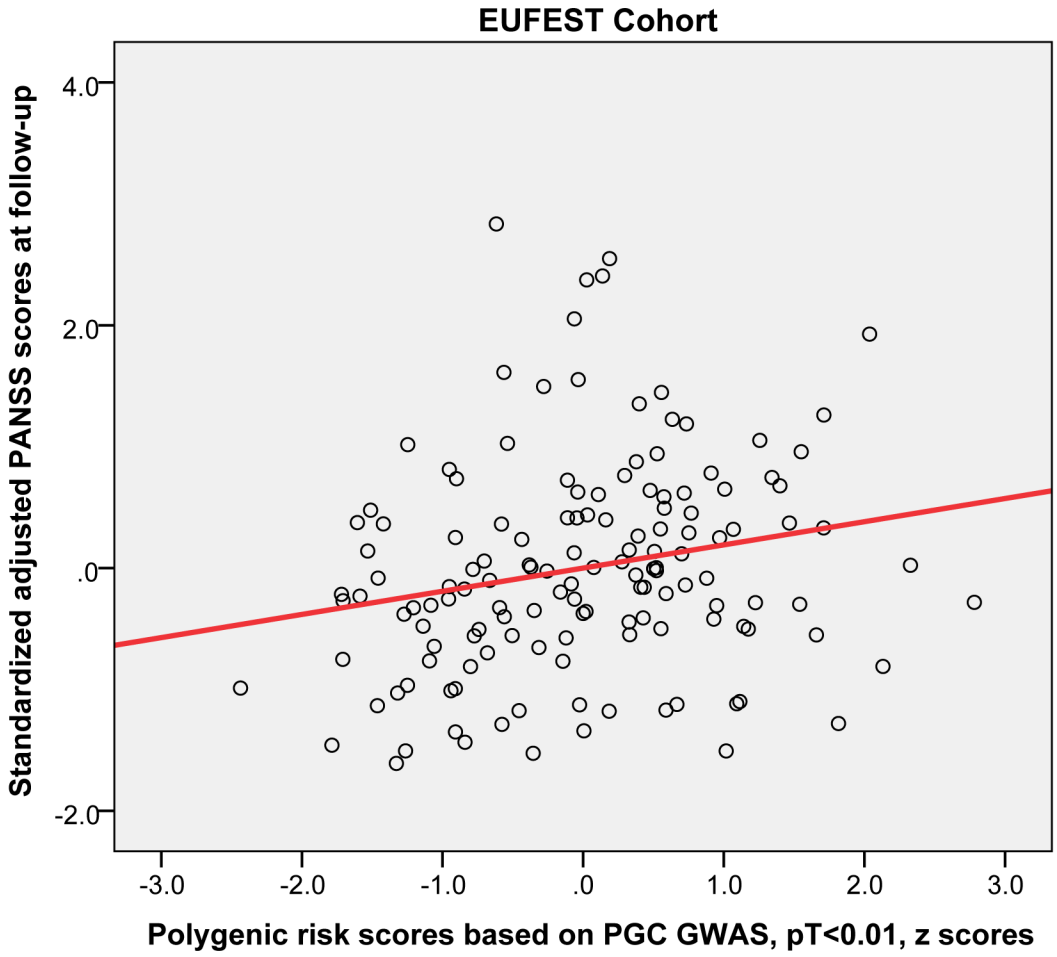
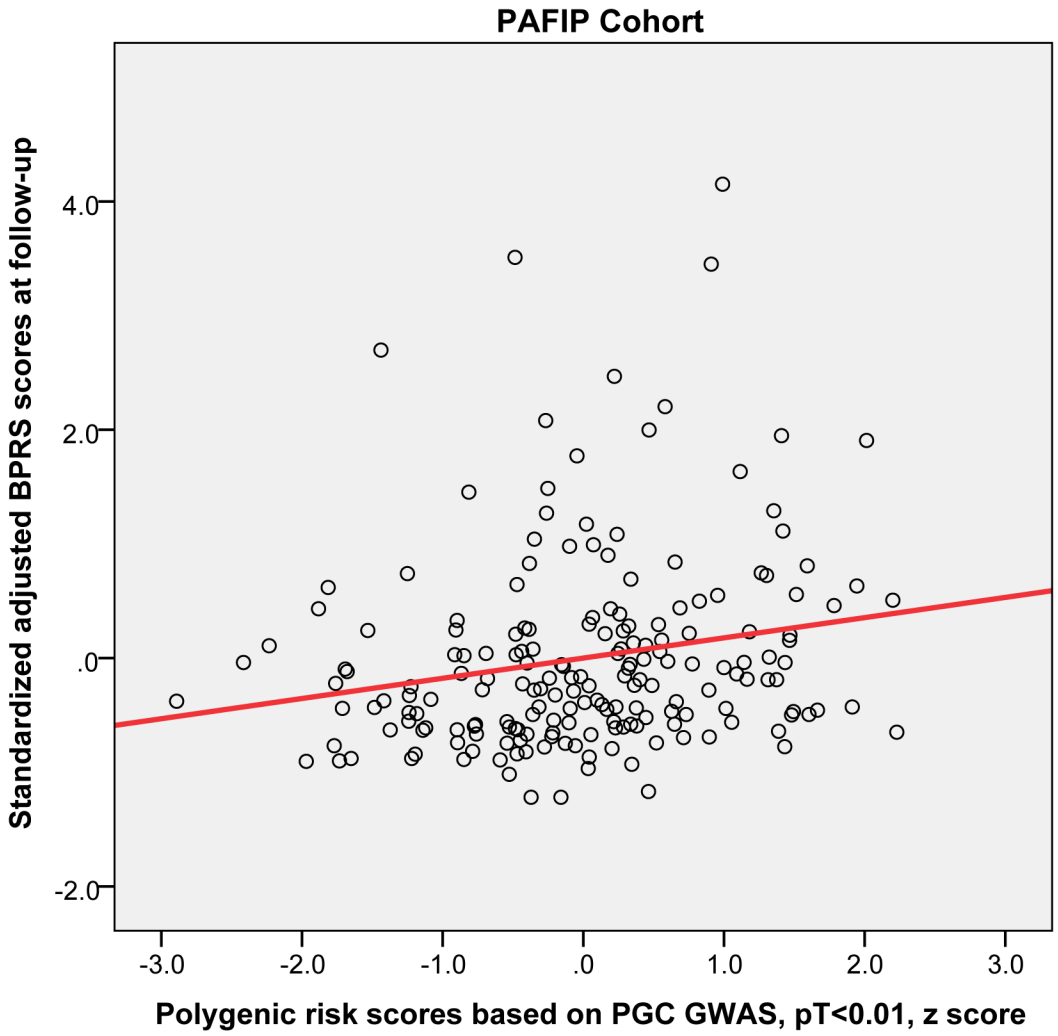


Figure 1.

PRS at different levels of p-value thresholds explained percentages of total variance in 12-week symptom scores controlling for baseline symptoms and other covariates in the discovery sample.







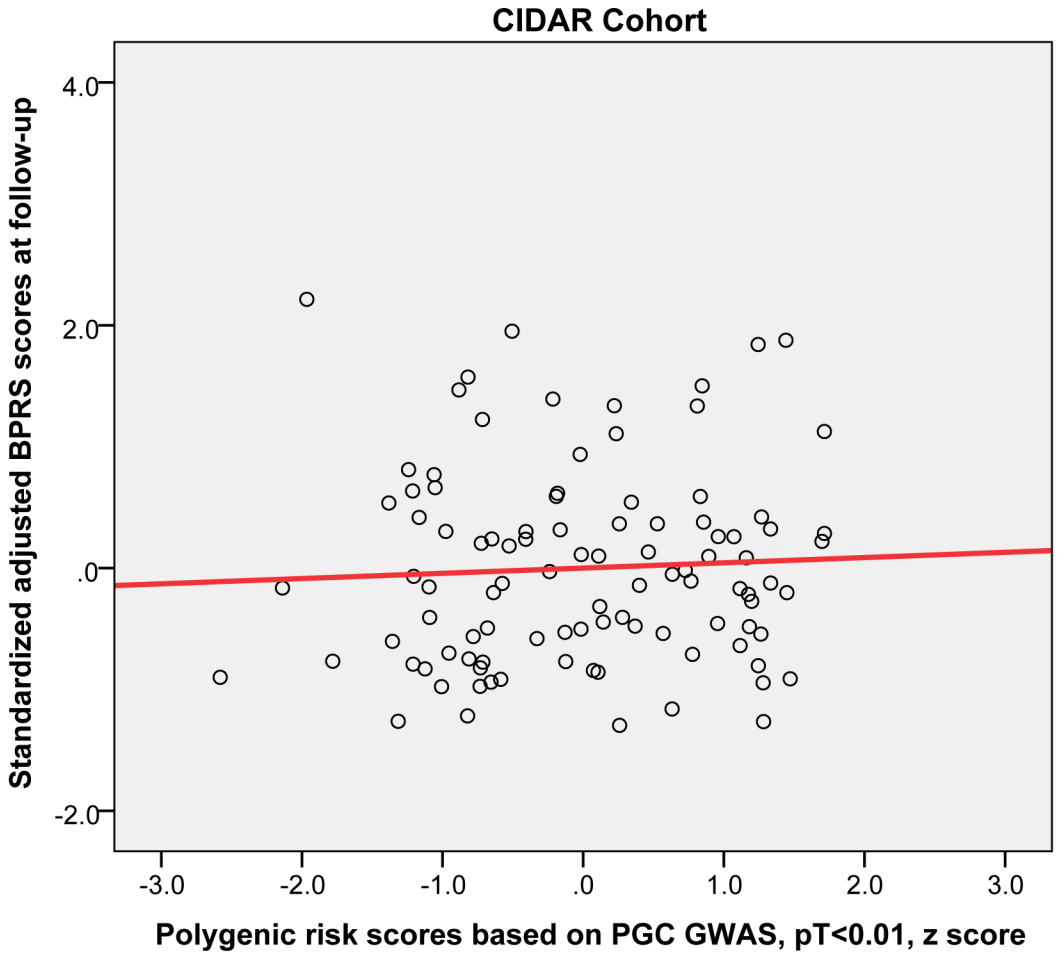


Figure 2.

Scatter plots with linear regression line of polygenic risk scores ($P_T < 0.01$) predicting standardized adjusted symptom scores at 12-week or 3-month follow-up controlling for age, sex, baseline symptom score, and genomic principal components (in the ZHH-FE and CIDAR cohorts). ZHH-FE: Zucker Hillside Hospital First Episode Schizophrenia trial; EUFEST: European First Episode Schizophrenia Trial; PAFIP: the Programa Asistencial Fases Iniciales de Psicosis de Cantabria, Spain; CIDAR: the clinical trial as part of the Center for Intervention Development and Applied Research at Zucker Hillside Hospital.

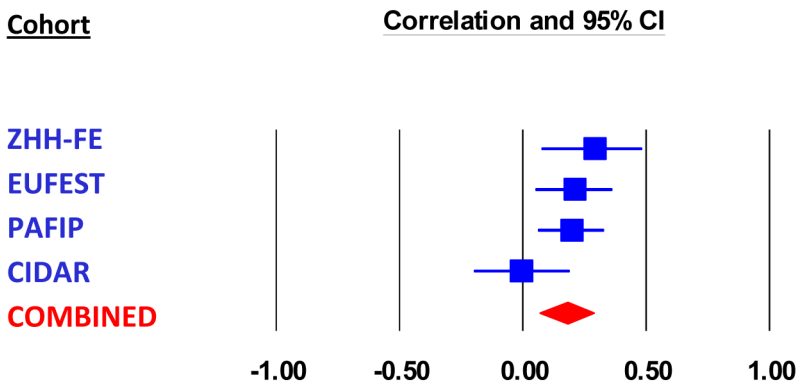


Figure 3.

Meta-analysis of the association between PRS at P_T <0.01 and symptom scores at 12-week follow-up in four cohorts. Effect size was partial correlation coefficient after controlling for age, sex, baseline symptom score, and genomic principal components (in the ZHH-FE and CIDAR cohorts). ZHH-FE: Zucker Hillside Hospital First Episode Schizophrenia trial; EUFEST: European First Episode Schizophrenia Trial; PAFIP: the Programa Asistencial Fases Iniciales de Psicosis de Cantabria, Spain; CIDAR: the clinical trial as part of the Center for Intervention Development and Applied Research at Zucker Hillside Hospital.

Table 1.

Demographic and descriptive data for the four cohorts included in the study.

Cohort	N	Age (M±SD)	% Male	% White	Symptom Rating Scale	# SNP's included in PRS at P_T<0.01
ZHH-FE	77	23.0±4.9	75%	39.0%	Derived BPRS items from SADS-C+PD	7736
EUFEST	141	25.6±5.2	60%	100%	PANSS	8903
PAFIP	192	31.8±10.2	52%	100%	BPRS	8634
CIDAR	100	21.5±5.1	75%	35.4%	BPRS	8110

Note: ZHH-FE: Zucker Hillside Hospital First Episode Schizophrenia trial; EUFEST: European First Episode Schizophrenia Trial; PAFIP: the Programa Asistencial Fases Iniciales de Psicosis de Cantabria, Spain; CIDAR: the clinical trial as part of the Center for Intervention Development and Applied Research at Zucker Hillside Hospital. BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Symptoms Scale; SADS-C+PD: Schedule for Affective Disorders and Schizophrenia Change Version with psychosis and disorganization items. PRS: Polygenic Risk Score. P_T: P-value threshold.

Table 2.

The results of hierarchical linear regression using PRS at P_T <0.01 to predict symptom scores at the 12-week or 3-month follow-up while controlling for age, sex, baseline symptom score, and genomic principal components (in the ZHH-FE and CIDAR cohorts).

	N	Beta	Partial r	p (2-tailed)	R^2 change
ZHH-FE	77	.680	.293	.013	8.1%
EUFEST	141	.190	.212	.012	3.5%
PAFIP	192	.195	.199	.006	3.7%
CIDAR	100	−.013	−.005	NS	0%

Note: ZHH-FE: Zucker Hillside Hospital First Episode Schizophrenia trial; EUFEST: European First Episode Schizophrenia Trial; PAFIP: the Programa Asistencial Fases Iniciales de Psicosis de Cantabria, Spain; CIDAR: the clinical trial as part of the Center for Intervention Development and Applied Research at Zucker Hillside Hospital. PRS: Polygenic Risk Score. P_T: P-value threshold.