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REVIEW

Transdiagnostic Effects of Schizophrenia Polygenic Scores on Treatment Outcomes in Major Psychiatric Disorders

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Video abstract

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Abstract: Schizophrenia polygenic risk scores (SCZ PRS) have emerged as important tools for modulating factors not only in schizophrenia but also in major psychiatric disorders, such as major depression (MDD) and bipolar disorder (BD). Initially developed to capture the common variant risk for SCZ, accumulating evidence highlights the transdiagnostic impact of SCZ PRS on clinical severity, treatment response, and functional outcomes. This review synthesizes recent findings on the relationship between SCZ PRS and treatment outcomes across SCZ, BD, and MDD. A higher SCZ PRS is associated with poorer treatment outcomes, including treatment resistance or non-remission to antidepressants in MDD, reduced antipsychotic response in SCZ, and diminished lithium efficacy in BD. SCZ PRS is also linked to persistent negative symptoms, cognitive impairments, and long-term illness severity in SCZ. While the effect sizes are generally modest, integration of SCZ PRS with environmental factors, multiomics, and neuroimaging may enhance predictive accuracy. Despite variability in reported associations, the overarching evidence supports a transdiagnostic influence of SCZ PRS on disease trajectories and treatment responses. As a promising component of precision psychiatry, SCZ PRS holds potential for guiding more targeted and effective interventions. Future research should focus on combining SCZ PRS with multimodal approaches to fully realize its clinical utility.

Keywords: schizophrenia, polygenic risk scores, major depressive disorder, bipolar disorder, treatment outcomes, precision psychiatry

Introduction

Schizophrenia (SCZ) is a highly heritable psychiatric disorder characterized by a heterogeneous clinical presentation, varying degrees of symptom severity, and a wide range of functional outcomes.[1] Advances in genome-wide association studies (GWAS) have enabled the identification of numerous common genetic variants associated with schizophrenia risk, and the aggregation of these variants into polygenic risk scores (PRS) has provided a quantitative index of genetic liability, which, in the most recent study, explained a relevant part of clinical variance.[2,3] While the SCZ PRS was initially developed to capture the common variants risk specific to schizophrenia, a growing body of evidence demonstrates that these polygenic influences extend beyond the traditional diagnostic boundaries of SCZ.[4–6] Psychiatric disorders, including SCZ, bipolar disorder (BD), and major depression (MDD), share overlapping genetic, neurobiological, and environmental risk factors. This overlap raises the possibility that PRS, developed for one disorder, may exert transdiagnostic effects on clinical outcomes. For instance, SCZ PRS may influence neural circuits involved in emotion regulation, cognitive processing, or stress response, which are implicated across major psychoses. Recent advancements in GWAS and the refinement of PRS methodologies have improved the predictive accuracy of SCZ PRS, enabling researchers to explore its role in treatment resistance, cognitive outcomes, and functional impairment across diagnostic categories. These developments underscore the need for a focused review synthesizing the latest evidence.

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Recent reviews provide a useful overview of the potential impact of PRS on treatment outcome,[7,8] however the broad approach in the reviews does not focus on SCZ PRS and does not include a substantial number of more recent studies across all major psychoses, moreover more recent studies used the enhanced prediction allowed by the latest SCZ PRS.[3]

In this narrative review, we aim to synthesize findings on the transdiagnostic effects of SCZ PRS, focusing on its impact on clinical outcomes in SCZ, BD, and MDD. By identifying shared patterns and unique effects, this review seeks to highlight the potential of SCZ PRS in advancing precision psychiatry.

Methods

This review synthesized evidence on the relationship between PRS SCZ and major psychiatric disorders treatment outcomes using a non-systematic approach. Studies were selected based on their relevance to PRS SCZ and treatment response, remission, or resistance, with the inclusion criteria focusing on original studies involving adults with MDD, BP, or SCZ. Non-original articles, such as reviews or commentaries, and studies unrelated to the treatment outcomes were excluded. A targeted search strategy on Pubmed and Google Scholar was employed using specific keywords ("polygenic score", "PRS", "risk profile score", "genetic risk score", "polygenic" "schizophrenia", "SCZ", "antidepress*", "treatment resistance", "bipolar", "BP", "treatment outcome", "antipsycho*", "stabiliz*", and "remission" in various combinations), including known studies identified through forward and backward citation searches and retrieved articles. Data extraction focused on the sample size, population characteristics, treatment outcomes, and statistical results for PRS SCZ. The findings were summarized without meta-analysis owing to heterogeneity in methods, populations, and outcome definitions, providing an overview of the current evidence on PRS SCZ and major psychiatric treatment outcomes.

Results

Major Depression

One of the earlier SCZ polygenic analyses of antidepressant response used two main cohorts, GENDEP (n=736) and STAR*D (n=1409), plus 5 other minor samples to explore whether SCZ PRS could predict improvement in depressive symptoms over 12 weeks or remission status following antidepressant therapy.[9] SCZ PRS was derived from the Psychiatric Genomics Consortium (PGC) data at multiple p-value thresholds and tested against symptom changes. Across both cohorts and a meta-analysis of seven pharmacogenetic studies (combined n=3756), SCZ PRS showed no significant association with improvement or remission. The strongest, albeit still non-significant, result for improvement was at the $p<0.0001$ threshold ($p=0.077$), and no threshold of SCZ PRS explained more than 3% of the variance in treatment outcomes, however in this early study 7 heterogeneous samples were meta analyzed using different treatments, assessment, duration of the trial and populations therefore adding possible stratification biases. More positive evidence followed,[10] when a population-based cohort from Generation Scotland (GS, n=3452) and the GENDEP cohort (n=761) were studied for antidepressant treatment resistance. Treatment resistance was defined as non-response to more than two antidepressants. GWAS of treatment resistance and PRS analyses were conducted, including those of the SCZ PRS. The study identified a nominal association between SCZ PRS and antidepressant treatment resistance in the meta-analysis (n=4213), significant at a p-value threshold of <0.01 ($p=0.027$, $\beta=0.011$, $R^2=0.0017$). However, the SCZ PRS did not predict the specific stages of resistance. While modest, this result indicated for the first time that a higher genetic liability for schizophrenia might be related to a reduced likelihood of responding to multiple antidepressants.

Similar results were observed for esketamine treatment, which included patients with treatment-resistant depression (TRD) received esketamine adjunctive therapy.[11] Combining participants from two Phase III clinical trials (TRANSFORM-3 and SUSTAIN-2, total n=527), the SCZ PRS was tested for remission, response (≥50% MADRS reduction), and percentage change in MADRS after 4 weeks of treatment. The SCZ PRS showed a nominal association with remission ($P=0.016$, standardized $\beta=-0.25$, $SE=0.10$) and response ($P=0.009$, standardized $\beta=-0.64$, $SE=0.25$); however, no association was detected for the percentage change in MADRS, with a trend in the opposite direction probably because of the baseline severity of the included patients and the rapid esketamine effect.

A larger population-based study examined data from the UK Biobank (UKB) and EXCEED cohorts on TRD.[12] Among UKB participants meeting MDD criteria (n=19,979), 13.2% were classified as TRD, and among EXCEED MDD

cases (n=1271), 13.49% met TRD criteria. When testing the PRS for SCZ, a non-significant trend was found to be associated with TRD (OR=1.04, 95% CI=0.99–1.09, p=0.14). The study's SNP-based heritability analysis suggested a higher genetic load for TRD than for non-TRD MDD and a positive but non-significant genetic correlation with schizophrenia PRS. The large size of the study and the direction of the trend support previous findings, though the heterogeneity inherent to population-based studies may introduce stratification effects that may not be detected at the analytic level.

The SCZ PRS was also investigated in a transdiagnostic youth mental health cohort (N =158).[13] Although the study's primary goal was to investigate clinical stage transitions and functioning, the study also considered the SCZ PRS in relation to diagnosis and follow-up outcomes. While the SCZ PRS predicted a baseline diagnosis of a psychotic disorder, it did not correlate with stage transition worsening. Although this study did not specifically focus on antidepressant outcomes, its findings suggest that the SCZ PRS can identify the risk of psychotic disorders, a factor indirectly related to antidepressant treatment resistance.

An interesting study focusing on TRD offered the perspective of personalized treatment based on the PRS. This study analyzed 1,148 patients diagnosed with MDD recruited by the European Group for the Study of Resistant Depression (GSRD).[14] Patients were classified as responders (n=279, 24.3%) and non-responders to one antidepressant (n=390, 33.97%). TRD was defined as non-response to at least two adequate treatments (n=479, 41.72%). The SCZ-PRS was nominally associated with nonresponse (p=0.003, empirical p=0.014) and explained 1.6% of the outcome variance. Patients in the highest SCZ-PRS quintile were more likely to be non-responders than those in the lowest quintile (OR=2.23, 95% CI=1.21–4.10, p=0.02). Furthermore, patients in the highest SCZ-PRS quintile had poor response rates, but benefited more from augmentation with antipsychotics, whereas those in the lowest SCZ-PRS quintile responded better to antidepressant monotherapy (p=0.009). Therefore, a higher SCZ-PRS may indicate a biologically distinct MDD subtype that is less responsive to antidepressant treatment but more responsive to antipsychotic augmentation. The clinical detail of the sample and the multicenter design of the study make it valuable when interpreting the findings. Results were confirmed by the same group in a subsequent meta-analysis across six European clinical cohorts (up to n=3,637 for non-response and n=3,184 for non-remission analyses).[15] The study found that SCZ PRS was nominally associated with non-remission (OR=1.16, 95% CI=1.01–1.33, P=0.035), but not with non-remission. The fact that the finding was replicated across multiple European samples strengthens the finding.

The effectiveness of electroconvulsive therapy (ECT) in treating severe depression has also been studied (n=266).[16] A higher PRS for SCZ strongly predicted better ECT outcomes. Patients with a higher PRS for SCZ showed a greater decrease in HDRS-17 scores (β=0.54, P<0.0001), higher remission rates, and greater response rates. These findings are robust across countries and across analyses. Importantly, this association persisted, even after excluding patients with psychotic features. Therefore, the results suggest that in very severe and resistant patients, the SCZ PRS may have a larger effect, probably because of the bias in mildly severe patients, where the magnitude of the antidepressant effect is usually lower. A partial confirmation was obtained from an independent sample.[17] This study analyzed 2,320 patients of European ancestry who underwent ECT for a major depressive episode. Improvement in the Clinical Global Impressions-Improvement (CGI-I) Scale was the primary outcome, while response (≥50% MADRS-S reduction) and remission (post-treatment MADRS-S ≤10) were secondary outcomes. SCZ PRS was not associated with improvement on CGI-I (OR=1.04, 95% CI=0.97–1.14, p=0.247) or response in the MADRS-S subsample (N=1,207, OR=1.05, 95% CI=0.93–1.19, p=0.401). However, the PRS for SCZ significantly predicted remission (OR=1.16, 95% CI=1.02–1.31, p=0.020, R^2=0.006). Interestingly, the direction of the effect of SCZ PRS was consistent with previous studies across all outcomes.

Concordant results were reported also for vortioxetine treatment. Nøhr et al[18] examined how various PRS, including SCZ PRS, influenced the response to vortioxetine or placebo in randomized controlled trials (n=1364) as well as in a self-reported cohort (n=642). In the self-report group, higher SCZ PRS was associated with poorer vortioxetine response (β= −0.28, P=0.0001), explaining approximately 3.6% of the variance, a comparatively large effect compared to previous PRS studies. However, in the clinical trial subset, the association between SCZ and PRS was not significant although it trended in the same direction. The discrepancy between self-reported and clinically assessed samples may underlie the

complexity of phenotype definitions and measurement methods for antidepressant outcomes, however the consistent direction supports the finding.

Perinatal antidepressant treatment is common and relatively understudied. A recent report investigated the trajectories of outcomes in Danish women with mood disorders (n=2316).[19] This study found no significant association between the SCZ PRS and patterns of antidepressant use (continuation, early discontinuation, etc) across the perinatal period. Instead, clinical and severity measures had a greater influence on the outcomes. In this case the specific perinatal sample may differ from previous studies samples also in terms of hormonal effects.

Electronic health record studies may offer the advantage of large sample sizes and are being increasingly used. A recent report leveraged large EHR systems and genetic data (VUMC BioVU, All Us, and MGB biobanks) to validate an antidepressant response algorithm and to test PRS associations.[20] Among European ancestry individuals, higher SCZ PRS was associated with worse antidepressant response (OR=1.05, $P=5.93\times10^{-4}$), remaining significant even after adjusting for depression diagnosis. Although the effect size was modest, the consistency across large independent cohorts and rigorous EHR-based phenotyping strengthen the evidence for SCZ PRS involvement in antidepressant outcome prediction.

Two other studies have reported negative findings. A Chinese Han sample of patients with MDD (n=912) was treated for 2 weeks and assessed by HAM-D17 reduction[21] and a sample of late-life depression (LLD) patients (n=342) was treated with venlafaxine for 12 weeks.[22] However the ethnicity, short duration and specific populations may represent confounding factors.

Consistent with previous findings, Mundy et al[23] studying early-onset MDD treatment trajectories over 7 years (n=10,577) from the Danish iPSYCH cohort and reported that the SCZ PRS was associated with a higher risk of later schizophrenia spectrum diagnoses, although the SCZ PRS was not associated with distinct MDD treatment trajectories (eg, persistent secondary care contact vs brief contact), however no direct antidepressant response was investigated.

In conclusion, several studies have reported nominal associations between poorer outcomes (eg, non-remission or treatment resistance) and higher SCZ PRS. Other studies, such as those on ECT and vortioxetine, have reported stronger associations. However, negative associations have also been reported. Factors such as treatment duration, age group, ethnic background, specificities of the sample, comorbidities, and method of outcome measurement (eg, clinician-rated vs self-reported) may influence the emergence of SCZ PRS effects. In any case, the direction of the higher SCZ PRS effect on worse antidepressant outcomes was almost consistent in the same direction, and two studies supported a liability to psychosis, independent of the original diagnosis (Table 1).

Schizophrenia

Schizophrenia outcome modulation by the SCZ PRS has been the most extensively studied. The most interesting study was a very long cohort study that explored the predictive role of the SCZ PRS in the 20-year course of illness in psychotic disorders.[5] The longitudinal Suffolk County Mental Health Project followed 249 first-admission psychosis patients and 205 never-psychotic controls over six assessments spanning 20 years. The SCZ PRS was derived from the PGC-2 GWAS data[24] and tested for associations with symptoms, cognition, illness severity, and diagnostic shifts. The results showed that the SCZ PRS was significantly higher in the psychosis group than in the control group. Within the psychosis cohort, SCZ PRS predicted persistent negative symptoms, particularly avolition ($\beta = 0.21$, $p < 0.05$), and greater illness severity as measured by the Global Assessment of Functioning ($\beta = -0.28$, $p < 0.01$). The SCZ PRS was negatively associated with cognition across follow-up ($\beta = -0.35$, $p < 0.01$) but did not predict cognitive decline. Importantly, the SCZ PRS predicted diagnostic shifts; participants initially diagnosed with affective psychosis were more likely to transition to non-affective psychosis over 20 years if they had higher SCZ PRS scores (AUC = 0.62). At the highest SCZ PRS decile, this diagnostic shift was detected with 68% accuracy. The SCZ PRS did not predict changes in positive symptoms, disorganization, or depression but showed robust associations with enduring cognitive deficits and negative symptoms. Although this study did not directly investigate treatment response, the results add to the landscape of the SCZ PRS effects.

One of the early small studies in 2016 analyzed 83 patients of European descent with schizophrenia or schizoaffective disorder to determine whether SCZ PRS predicted standardized antipsychotic doses (measured as PM%, CPZe, and

Table 1 Summary of Studies Investigating SCZ PRS and Antidepressant Response

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Wigmore et al, 2020 [10]	SCZ PRS and AD resistance	Population-based, retrospective	Antidepressants (≥2 non-responses for TR)	GS=3452 (TRD=250, Controls=3202); GENDEP=761 (TRD=109, Controls=668)	SCZ PRS nominally associated with treatment resistance (P=0.027, β=0.011, R^2=0.0017). No significant association with stages of resistance.	Suggests shared genetic architecture between schizophrenia and antidepressant resistance.
Li et al, 2020 [11]	SCZ PRS in esketamine response	Phase III trials, 4 weeks	Esketamine	TRD=527 (TRANSFORM-3=95; SUSTAIN-2=432)	SCZ PRS nominally associated with remission (P=0.016, β=-0.25). Not associated with MADRS percentage change or response.	Indicates possible genetic overlap between schizophrenia liability and esketamine remission.
Fabbri et al, 2021 [12]	SCZ PRS in TRD	Retrospective primary care records	Antidepressants (≥2 switches define TRD)	UKB: MDD=19979 (TRD=2430); EXCEED: MDD=1271 (TRD=159)	SCZ PRS non-significant trend with TRD (OR=1.04, P=0.14). TRD showed higher SNP-heritability (0.25) vs non-TRD (0.19).	SCZ genetic liability not strongly linked to TRD. TRD more heritable.
García-González et al, 2017 [9]	SCZ PRS in AD response	Pharmacogenetic cohorts, up to 12 weeks	Various antidepressants	GENDEP=736; STAR*D=1409; Other studies. Total ~3756	SCZ PRS did not predict improvement or remission. Most significant trend p=0.077, explained <3% variance.	No clear SCZ PRS influence on antidepressant response.
Fanelli et al, 2022 [15]	SCZ PRS in AD response	Meta-analysis (6 European cohorts)	Various antidepressants	Non-response analyses n=3637; Non-remission n=3184	SCZ PRS nominally associated with non-remission (OR=1.16, P=0.035, R^2=0.37%). Not associated with non-response.	SCZ genetic liability may slightly decrease remission odds.
Luykx et al, 2022 [16]	SCZ PRS and ECT outcomes	Observational, multi-country	ECT for depression (HDRS-17 measured)	After QC=266 (Ireland=122, Belgium=63, Netherlands=81)	SCZ PRS associated with HDRS improvement (β=0.54, P<0.0001, R^2=6.94%) and remission (P=0.0018).	Higher SCZ PRS predicts better ECT outcomes.
Nøhr et al, 2022 [18]	SCZ PRS in vortioxetine/ placebo	7 RCTs pooled	Vortioxetine vs placebo	Clinical:1364 (vort=907, plac=455); Self-report:642	SCZ PRS associated with poorer self-reported vortioxetine response (β=-0.28, P=0.0001, R^2=3.6%). No placebo association.	SCZ genetic load may reduce subjective vortioxetine effectiveness.
Liu et al, 2024 [19]	SCZ PRS in MDD perinatal trajectories	Registry-based, observational	Antidepressants (≥6m before pregnancy)	n=2316 MDD women	SCZ PRS not associated with any treatment trajectory.	SCZ PRS does not influence perinatal antidepressant outcome. Clinical severity factors modulate outcome.
Sealock et al, 2024 [20]	SCZ PRS and first AD trial	EHR-based retrospective	First-line antidepressants	VUMC ~315935 with AD data; genetic subset=30152	Higher SCZ PRS associated with worse response (OR=1.05, P=5.93×10^{-4}). Association remains after adjusting for depression.	SCZ genetic liability modulates antidepressant response.
Shao et al, 2025 [21]	SCZ PRS in AD response	Prospective, 2-week treatment	Antidepressants	n=912 Han Chinese after QC	SCZ PRS not significantly associated with 2-week HAM-D17 reduction (P>0.05).	SCZ PRS not relevant for short-term antidepressant response in this sample.
Mundy et al, 2024 [23]	SCZ PRS in early-onset MDD outcome	Danish registry, 7-year follow-up	Secondary care MDD treatment	n=10577	SCZ PRS not linked to MDD treatment trajectories. SCZ PRS (OR=1.26, P<0.0001) predicted later schizophrenia spectrum diagnosis.	SCZ PRS not modulating MDD course but may modulate future schizophrenia risk.

(*Continued*)

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Table 1 (Continued).

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Elsheikh et al, 2024 [22]	SCZ PRS in late-life response	Open-label, 12 weeks	Venlafaxine XR 37.5–300 mg/day	n=342 older adults (≥60) with MDD	SCZ PRS not associated with remission (OR=0.84, P=0.36) or improvement (β=-2.92,P=0.57).	SCZ PRS not affecting venlafaxine response in late-life depression.
Crouse et al, 2021 [13]	SCZ PRS in youth mental health	Transdiagnostic, ~40.8m follow-up	Various early-intervention services	n=158 youth (12–30), various diagnoses	SCZ PRS associated with baseline psychotic disorder (OR=1.68, P=0.020), not with functioning or clinical stage transitions.	SCZ PRS linked to psychosis diagnosis but not functional outcomes.
Fanelli et al, 2021 [14]	SCZ PRS in AD response	Observational study	Various antidepressants	MDD=1148 (Resp=279, Non-resp=390, TRD=479)	SCZ PRS nominally associated with non-response (p=0.003, R^2=1.6%), highest quintile OR=2.23.	High SCZ PRS may indicate MDD subtype resistant to antidepressants. Small effect size.
Sigström et al, 2022 [17]	SCZ PRS and ECT outcome	Observational ECT study	ECT for MDD (CGI-I, MADRS-S)	N=2320 ECT, MADRS-S subset=1207	SCZ PRS not associated with CGI-I improvement/ response. Associated with remission on MADRS-S (OR=1.16, P=0.020,R^2=0.006).	Minimal SCZ PRS effect on ECT remission. Low variance explained.

Abbreviation: AD, Antidepressant(s); ADHD, Attention-Deficit/Hyperactivity Disorder; BD, Bipolar Disorder; CD, Cross-Disorder; CGI-I, Clinical Global Impression–Improvement; ECT, Electroconvulsive Therapy; HER, Electronic Health Record; GENDEP, Genome-Based Therapeutic Drugs for Depression; GS, Generation Scotland: Scottish Family Health Study; GWAS, Genome-Wide Association Study; HAM-D/HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, Major Depressive Disorder; OR, Odds Ratio; PCs = Principal Components; QC = Quality Control; RCT, Randomized Controlled Trial; R^2, Coefficient of Determination; SCZ PRS, Schizophrenia Polygenic Risk Score; SNP, Single Nucleotide Polymorphism; TRD, Treatment-Resistant Depression; VUMC, Vanderbilt University Medical Center; XR, Extended Release.

DDD) or symptom severity.[25] The authors found no significant association (p=0.691 for PM%). However, alcohol abuse and dependence correlated with higher doses. The small size of the study is a strong limitation. In the same year, a larger study included 612 patients with schizophrenia from the Australian MGS cohort, and defined treatment-resistant schizophrenia (TRS) based on the failure of two adequate antipsychotic trials.[26] They found no significant association between SCZ PRS (p=0.181) and TRS but identified that TRS patients had a higher rare duplication burden genome-wide (OR=1.05, p=0.002), earlier illness onset, fewer years of schooling, and more severe symptoms than those without TRS. However, the trend, in a relatively small sample, was in the same direction as the higher SCZ PRS and TRS.

The TRS was also examined in 862 Danish individuals diagnosed with schizophrenia to assess its association with SCZ PRS, which was defined as clozapine use or hospitalization.[27] 21% met TRS criteria and, though a 1-SD increase in PRS-SZ did not significantly raise TRS risk (HR=1.13, p=0.58), the non-significant trend was in the same direction.

Treatment naive patients are a potentially interesting sample to study, and in 2018 a study investigated 60 antipsychotic-naive first-episode psychosis (FEP) patients and 60 controls in São Paulo, Brazil.[28] Using the SCZ PRS, they found baseline associations with higher excitement (p=0.0003), depressive symptom trends, plus lower functioning. After approximately nine weeks of risperidone treatment, SCZ PRS was negatively associated with depressive symptoms, but also negatively associated with symptom improvement, though not significantly. In 2018, Li et al[29] assessed two lurasidone RCTs with 171 Caucasian and 131 African-American schizophrenia patients. SCZ PRS predicted response in Caucasians, explaining as much as 7% of the variance in positive symptom improvement (p=0.002), and implicating neurodevelopmental, synaptic, and immune genes.

A larger study examined 510 first-episode psychosis patients across four cohorts (ZHH, EUFEST, PAFIP, CIDAR) and found that higher SCZ PRS predicted poorer 12-week antipsychotic response, explaining up to 8.1% variance in one cohort and consistently ~3-4% in others.[30] Patients with low SCZ PRS showed better treatment response rates (61.8% vs 45.8%). The magnitude of the reported effects is interesting because it gets closer to clinical relevance. Negative results have also been reported, but again, in the same detrimental direction as a high SCZ PRS and worse outcomes. A 2019 study analyzed population based sample 24,706 Swedish patients with schizophrenia, defining TRS as clozapine use or polypharmacy.[31] SCZ PRS showed a non-significant trend with TRS (p=0.067), and a higher family history burden and lower premorbid IQ increased the TRS risk. In a larger community study that examined 4,475 Danish-born schizophrenia patients, it was observed that each SD increase in SCZ PRS increased the TRS risk by 11%, which was more pronounced in urban-born patients (HR=1.39), suggesting a potential gene-environment interplay.[32]

With a broader focus, in 2020, Werner et al[33] studied 321 schizophrenia spectrum disorder (SSD) patients and found higher SCZ PRS at p=0.01 threshold associated with TRS (p=0.003, OR=1.5). This model showed good specificity (90.6%) but low sensitivity (29.6%), confirming prior evidence that PRS contributes modestly but significantly to TRS prediction.

By 2022, multiple studies will integrate the SCZ PRS into a broader model. Facal et al[34] focused on 427 schizophrenia patients and introduced the exprAP PRS, constructed from SNPs acting as eQTLs under antipsychotic influence. The ExprAP PRS was strongly associated with hospital readmissions (OR=1.48) and explained more variance than the SCZ PRS alone; however, SCZ PRS was also associated with hospital readmissions (p=0.036). Another combination was investigated in the same year, this time with a pharmacokinetic variant. Okhuijsen-Pfeifer et al[35] investigated 684 patients who received clozapine. A higher PRS for SCZ was associated with lower symptom severity (R^2=1.85%), and CYP2C19 activity also predicted severity in a synergistic manner, however the analysis on clozapine only treated subjects may not be informative on overall outcome effects. The largest TRS study was conducted during the same year. Pardiñas et al[36] analyzed 10,501 TRS and 20,325 patients without TRS. The SCZ PRS predicted TRS explaining ~1-2% variance (p=0.001), the large sample size of this study should value the reported results. Similar results, but in a much smaller sample, were reported in the same year by a study that examined 63 TRS and 111 non-TRS patients, noting higher SCZ PRS among TRS individuals (p=0.0858) and a 2.42-fold increase in TRS risk for the top deciles.[37] Network analyses highlighted synaptic and developmental pathways.

Another combination study in the same year used a small sample of 57 first-episode schizophrenia patients, integrating PRS and resting-state functional connectivity (rsFC).[38] SCZ PRS explained an incremental 9% of the variance

in the 6-week risperidone response compared to rsFC alone, suggesting that combining genetics with neuroimaging biomarkers can potentially enhance predictive power.

More recently, Rodriguez et al[39] studied 573 FEP and 1005 controls and found that the SCZ PRS was strongest for SSD (OR=2.08), especially in the lower environmental exposure strata. No significant gene-environment interactions emerged, but additive effects supported the liability threshold model, though not directly investigating treatment outcome, this study adds to the potential effects of SCZ PRS. In the same year, Lenk et al[40] found that SCZ PRS was strongly linked to the TRS (OR=1.4), which is consistent with the results of several earlier studies. Smoking also predicted TRS (OR=1.4).

A complex combination model was tested in 2023 by a study that integrated multiomics in 2307 SCZ patients from the CAPOC and 1379 from the CAPEC trials.[41] The study confirmed that SCZ PRS correlated negatively with antipsychotic response (r=−0.045, p=0.032) and identified genetic-epigenetic interactions in six SCZ risk genes that influence response. Their predictive model using PRS, GRS, and proxyDNAm achieved an AUC>0.85 in validation.

Although previous studies did not show a clear association between SCZ PRS and dose, a larger and more recent study did. Kappel et al[42] studied three TRS clozapine-treated cohorts (total ~4459 individuals) and showed that SCZ PRS was associated with higher clozapine doses (p=0.001) and >600 mg/day dosing odds. This was consistent with the study by Lin et al,[43] who found a higher SCZ PRS in SSD patients on clozapine and a dose-response effect. Again, though not directly investigating treatment outcome, this study may suggest that the need of higher clozapine doses could indicate a higher resistance.

The most recent study,[44] examined 460 European patients with schizophrenia, schizoaffective disorder, bipolar disorder, and other diagnoses. They tested both PRS response (11 SNPs from an antipsychotic response GWAS) and SCZ PRS. While PRSresponse significantly predicted antipsychotic efficacy (OR=1.14, p=0.01 for the whole cohort), especially in schizophrenia (OR=1.27, p=0.01), SCZ PRS was not significant, though in the same direction as a trend (p=0.09). However, sensitivity and specificity remained suboptimal (approximately 60%).

Overall, across nearly a decade of studies, the SCZ PRS has consistently emerged as a modest but statistically significant predictor of antipsychotic response, treatment resistance, and related phenotypes in schizophrenia. Integrations with environmental factors, other psychiatric PRS, rare variants, multiomics, and neuroimaging may improve the explanatory power (Table 2).

Bipolar Disorder

Bipolar disorders have been much less studied than MDD and SCZ; however, a number of recent studies have been published. In a large CONLIGEN collaborative study, the relationship between SCZ PRS and lithium treatment response in BD was examined by analyzing 2,586 patients who were genotyped and assessed using the ALDA scale for long-term lithium response.[45] A higher SCZ-PRS predicted poorer lithium response, with lower SCZ PRS patients having higher odds of responding well. Fifteen genetic loci with overlapping effects on schizophrenia risk and lithium response were identified, notably involving the HLA antigen complex and inflammatory cytokines (TNF, IL-4, and IFNγ). The same sample was studied for possible increased prediction of combined factors and machine learning methods. In a subsample of 2,283 BD patients, the SCZ PRS ($p = 0.0005$; partial $R^2 = 0.82\%$) and MDD PRS ($p = 0.009$; partial $R^2 = 0.47\%$) both predicted a poorer lithium response, while the BD PRS did not.[46] Moreover, a meta-analytic PRS (MET2) combining SCZ and MDD variants performed better ($p = 0.0003$; partial $R^2 = 0.91\%$) than the single-trait or triple-trait (SCZ, MDD, BD) PRS. Patients in the top MET2 PRS decile had 2.54 times higher odds of a poor response than those in the lowest decile. This suggests that the lithium response in BD might be driven more by genetic architectures shared with SCZ and MDD than by BD itself. Pathway analyses have implicated histone biology and metabolic pathways. Complex interplay was studied in the same sample using a machine learning approach in a subsample of 1,034 BD patients.[47] The model used the SCZ PRS, MDD PRS, and the combined MDD+SCZ meta-PRS. Unimodal PRS models explained up to 2% of the variance, whereas adding clinical variables improved performance by up to 7.4%. Stratifying patients by PRS groups and then applying clinical predictors boosted the explained variance to 13.7% ($p = 0.0001$) for the combined MDD+SCZ meta-PRS. Patients with lower SCZ and MDD polygenic load were 1.68 times more likely to respond to lithium than those with higher polygenic burdens.

Table 2 Summary of Studies Investigating SCZ PRS and SCZ outcome

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Jonas et al, 2019 [5]	SCZ PRS and 20-year course	Longitudinal, 20-year follow-up	No active treatment (observational)	Psychosis=249, Controls=205	SCZ PRS higher in psychosis, predicted persistent negative symptoms (β=0.21, p<0.05), worse GAF (β=-0.28, p<0.01), poorer cognition (2y β=-0.29, p<0.05; 20y β=-0.35, p<0.01), Affective→Non affective shift (AUC=0.62).	SCZ PRS predicts long-term symptom severity, cognition, and diagnostic shifts.
De Pieri et al, 2024 [44]	PRS and AP response	Real-world cohort, 1-year	Various AP	n=460 patients (SCZ, SZA, BP, others); SCZ +SZA=176, SCZ=149	PRSresponse associated with response: OR=1.14 (95%CI:1.03–1.26, p=0.01), poor sensitivity/ specificity. SCZ PRS not significant.	PRSresponse may predict outcomes.
Guo et al, 2023 [41]	SCZ PRS and AP response	Randomized trials, 6-8 weeks	Olanzapine, risperidone, aripiprazole, quetiapine, ziprasidone, haloperidol, perphenazine; doses not specified	CAPOC: n=2307 SCZ; CAPEC: n=1379 SCZ	PRS-SCZ correlates with response (r=-0.045, p=0.032). Combined model AUC=0.874 and 0.851.	Integrating PRS and multiomics improves prediction of antipsychotic response.
Okhuijsen-Pfeifer et al, 2022 [35]	SCZ PRS and severity in clozapine	Cross-sectional, multiple cohorts	Clozapine	n=684 clozapine-treated SSD	SCZ PRS associated with lower severity ($p=1.03\times10^{-3}$, R^2=1.85%). Top decile odds=2.26 ($p=3.96\times10^{-3}$). CYP2C19 activity OR=1.59 ($p=8.44\times10^{-3}$).	Higher SCZ PRS and CYP2C19 activity predict better clozapine outcome.
Santoro et al, 2018 [28]	SCZ PRS and symptom change	Longitudinal, ~9 weeks	Risperidone ~9.03±2.76 weeks	FEP n=60, controls n=60	Baseline: SCZ PRS→higher excitement (B=566.7, p=0.0003). Post-treatment: SCZ PRS→reduced depressive symptoms (B=-1800.2, p=0.0004).	SCZ PRS influences symptom dimensions and improvement patterns.
Zhang et al, 2019 [30]	SCZ PRS and FEP response	Multicohort, up to 12 weeks	Risperidone, olanzapine, haloperidol, aripiprazole, quetiapine, ziprasidone; doses not specified	n=510 FEP across 4 cohorts	Higher SCZ PRS predicts poorer response: meta partial r=0.18, p=0.002. Low SCZ PRS response=61.8% vs high=45.8%, OR=1.91.	SCZ PRS is a prognostic biomarker for antipsychotic response.
Li et al, 2018 [29]	SCZ PRS and lurasidone	2 RCTs, double-blind, 6 weeks	Lurasidone	n=171 Caucasian SCZ, n=131 African American SCZ	SCZ PRS predicts greater improvement in positive symptoms (p=0.002, ~7% variance).	SCZ PRS associates with lurasidone response.

(*Continued*)

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Table 2 (Continued).

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Hettige et al, 2016 [25]	PRS and antipsychotic dosage	Cross-sectional	Various antipsychotics, standardized dose metrics (PM%,CPZe,DDD)	n=83 SCZ/SZA European descent	No association between PRS and dosage (p≥0.512).	PRS does not predict dose requirement in this small sample.
Kappel et al, 2023 [42]	SCZ PRS and clozapine dose	Observational, multiple cohorts	Clozapine; >600 mg/day	CLOZUK2: n=3133, CLOZUK3: n=909, Norwegian: n=417	Higher SCZ PRS→higher dose (CLOZUK2 β=12.22, p=0.001). OR for high dose=1.279 (95% CI:1.076–1.522, p=0.005).	Genetic liability correlates with higher clozapine dosing needs.
Lin et al, 2023 [43]	SCZ PRS and clozapine use	Genetic association study, 6-year follow-up	Clozapine, other APs	n=2344 (SCZ Spectrum, relatives, controls), 557 clozapine users	PRS-SCZ OR=1.41 ($p=2.98\times10^{-6}$) for clozapine use. Highest quintile OR=2.50.	Higher genetic load increases likelihood of clozapine treatment.
Talarico et al, 2022 [37]	SCZ PRS and TRS	Case-control TRS vs non-TRS	Various APs	n=63 TRS, n=111 non-TRS	Top PRS deciles increase TRS risk by 2.42-fold (p=0.0336).	SCZ PRS contributes to TRS risk.
Gasse et al, 2019 [32]	SCZ PRS, urbanicity, and TRS	Population-based cohort (1996–2013)	Various APs, TRS includes clozapine initiation	n=4475 SCZ in Danish registers	Each SD SCZ PRS →11% TRS increase (HR=1.11). In capital area HR=1.39.	SCZ PRS and urban birthplace interact in TRS risk.
Werner et al, 2020 [33]	SCZ PRS and TR in SCZ spectrum	Naturalistic, cross-sectional	Various APs	n=321 SCZ spectrum (TR=108)	SCZ PRS p=0.01: OR=1.5 (p=0.003). Sensitivity=29.6%, specificity=90.6%.	SCZ PRS indicates TR risk, though with modest sensitivity.
Pardiñas et al, 2022 [36]	SCZ PRS and TRS	GWAS (TRS vs non-TRS)	Clozapine use TRS	TRS=10,501; non-TRS=20,325; controls=54,664	No genome-wide hits. PRS explains 2.03% TRS variance (p=0.001).	SCZ PRS associated with TRS but low predictive power.
Wimberley et al, 2017 [27]	SCZ PRS and TRS	Population-based cohort (1999–2007)	Various APs; TRS includes clozapine criteria	n=862 SCZ in Denmark	1-SD PRS↑: HR=1.13 (95%CI:0.95–1.35), not significant.	SCZ PRS not sufficient to predict TRS but in consistent direction.

Martin et al, 2016 [26]	Rare duplication burden in TRS	Cross-sectional	Various APs	n=612 SCZ	SCZ PRS not significant (OR 1.03, 95% CI 0.97–1.10, p=0.181).	SCZ PRS not sufficient to predict TRS but in consistent direction.
Kowalec et al, 2021 [31]	Family history, IQ, SCZ PRS in TRS	Registry-based large sample	TRS by clozapine or polypharmacy	n=24706 SCZ; genomic subset=4936	Family history aOR=1.31 ($p=4.8\times10^{-3}$). SCZ PRS as a trend (aOR= 1.07, p=0.067).	Familial and developmental factors outweigh SCZ PRS in TRS risk.
Facal et al, 2022 [34]	PRS from antipsychotic-responsive genes and admissions	Retrospective chart review	Various APs	n=427 SCZ	ExprAP PRS OR=1.48 (p=0.0085) for readmission. SCZ PRS also associated (p=0.036).	Both SCZ PRS and PRS focusing on AP-altered gene expression predicts hospitalization risk.
Lenk et al, 2024 [40]	SCZ PRS and TRS	Cross-sectional	Clozapine vs risperidone (TDM confirmed)	n=1286 (TRS=478)	SCZ PRS OR=1.4 ($p=2.1\times10^{-6}$).	SCZ PRS linked to TRS.
Mehta et al, 2024 [38]	SCZ PRS + rsFC in response	Longitudinal, 6 weeks	Risperidone	n=57 FEP, 43 with imaging/ genetics	SCZ PRS adds 9% variance to prediction; rsFC adds total up to $R^2=0.53$ ($p<0.0001$).	Combining SCZ PRS and neuroimaging improves prediction of short-term response.
Rodriguez et al, 2024 [39]	SCZ PRS and environment in FEP	Case-control	Naturalistic	n=573 FEP (409 SCZ spectrum, 164 AP), n=1005 controls	SCZ PRS OR=2.08 (p<0.001) for SCZ spectrum. Additive effects with environment, no significant GxE.	SCZ PRS and environmental factors additively influence psychosis liability.

Abbreviation: AP, Antipsychotic(s); AUC, Area under the curve; BP, Bipolar disorder; CGI, Clinical Global Impression; CI, Confidence interval; CpGe, Chlorpromazine equivalents; DDD, Defined daily dose; eQTL, Expression quantitative trait loci; FEP, First-episode psychosis; GWAS, Genome-wide association study; HR, Hazard ratio; OR, Odds ratio; PANSS, Positive and Negative Syndrome Scale; PM%, Percentage of maximum dose; PRS,Polygenic risk score; R^2, Coefficient of determination; rsFC, Resting-state functional connectivity; SCZ PRS, Schizophrenia polygenic risk score; SCZ, Schizophrenia; SNP, Single nucleotide polymorphism; SZA, Schizoaffective disorder; TDM,Therapeutic drug monitoring; TRS, Treatment-resistant schizophrenia.

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Treatment outcome is also correlated with phenotypic features, in a recent paper Grigoroiu-Serbanescu et al[48] examined 1,878 BP-I cases and 2,751 controls of European ancestry. The SCZ PRS significantly predicted an earlier age of onset for BP-I, depression ($\beta = -1.2$, p = 1.96E-04), and mania ($\beta = -1.34$, p = 4.82E-05), as well as a greater likelihood of psychosis (OR = 1.589, p = 1.53E-42) and incongruent psychosis (OR = 1.591, p = 3.30E-16). Moreover, the SCZ PRS was negatively associated with rapid cycling (OR = 0.637, p = 2.13E-09). While the SCZ PRS alone offered modest predictive power (AUC=0.625 for psychosis), combining it with clinical variables substantially improved the predictions (AUC=0.785). Pathway analyses revealed a significant enrichment of genes related to brain development, immune processes, mitochondria, and dopamine signaling. These findings complement those of earlier studies by suggesting that SCZ PRS may influence not only the treatment response in BD but also phenotypic traits linked with severity.

Song et al[49] explored the subphenotypes of BD in two large cohorts (n = 5180 from SWEBIC, n = 2577 from BDRN) and tested BD BD-PRS, SCZ-PRS, and MDD PRS with inter-episode remission, global functioning (GAF), psychotic symptoms, and comorbid anxiety disorders. SCZ PRS was negatively associated with inter-episode remission (meta OR = 0.91, $p = 6.98 \times 10^{-4}$). SCZ-PRS also increased the likelihood of psychotic symptoms during mood episodes (OR = 1.19, $p = 2.07 \times 10^{-8}$). Although a negative trend was observed for GAF functioning ($\beta = -0.49$, p = 0.01), it did not survive the correction.

In conclusion, despite the relatively low number of studies, SCZ PRS contributes to predicting more severe psychotic presentations within BD, which may lead to a poor lithium response, persistent negative symptoms, or difficulty achieving remission (Table 3).

Discussion

The findings summarized in this review strongly support that the SCZ PRS exerts a potentially useful, albeit modest, influence on psychiatric phenotypes, not only in SCZ itself but also in MDD and BD. Indeed SCZ PRS include gene variants that have been also associated with MDD and BD, with overlapping physiopathology, including excitatory hippocampal neurons and GABAergic neurons, and with a strong genetic correlation across the three disorders.[50–52] By examining treatment outcomes, symptom patterns, and illness trajectories, several studies have repeatedly observed that the SCZ PRS confers varying degrees of risk across traditional diagnostic boundaries. Although the effect sizes are often small, the consistency of these observations highlights a transdiagnostic genetic influence and the potential utility of the SCZ PRS for guiding precision medicine strategies in psychiatry (Figure 1).

A large body of evidence comes from studies that focus on the antipsychotic treatment response in schizophrenia. The SCZ PRS generally predicted poorer responses to standard antipsychotics, especially in the first-episode psychosis cohorts. In addition, the SCZ PRS was associated with more persistent negative symptoms, greater illness severity, and poorer cognitive performance over 20 years.

Transdiagnostic effects emerge clearly when we consider how PRS in SCZ is related to treatment response in bipolar disorder. Relatively few but large studies have consistently demonstrated that a higher PRS for SCZ predicts poorer lithium response in patients with BD.

In MDD, the evidence is somewhat more limited and complex, partly due to fewer direct investigations and the larger heterogeneity of the studies. However, some studies have suggested that the SCZ PRS may also affect treatment outcomes in patients with MDD. Several studies have identified nominal or suggestive associations between PRS in SCZ and poorer antidepressant responses, although these have often failed to achieve robust statistical significance or survive correction for multiple tests. Nonetheless, when considering the entire body of evidence, even these non-significant or borderline results align with the broader view that PRS in SCZ generally correlates with more severe or less treatable illness. It remains possible that larger and more refined analyses, especially those integrating multimodal data (eg, imaging and epigenetics), may elucidate the role of the SCZ PRS in MDD treatment response.

The impact of SCZ PRS on phenotypes such as treatment-resistant schizophrenia (TRS) also underscores transdiagnostic implications. TRS represents one of the most refractory states within the psychotic disorder spectrum, and multiple studies have shown that individuals with TRS tend to have a higher PRS for SCZ. Although TRS is categorized within the schizophrenia spectrum, these results are consistent with the general idea that SCZ genetic risk variants influence the severity and response to treatment, rather than diagnostic boundaries.

Table 3 Summary of Studies Investigating SCZ PRS and BD outcome

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Amare et al, 2018 [45]	SCZ PRS and lithium response	Retrospective	Lithium (long-term)	BD=2586	Higher SCZ PRS → poorer lithium response (0.8% variance). Lower SCZ PRS increases odds of good response (OR up to 3.46). HLA/ inflammation genes implicated.	SCZ PRS predicts lithium non-response.
Schubert et al, 2021 [46]	Multi PRS and lithium response	Retrospective	Lithium (long-term)	BD=2283	SCZ PRS (p=0.0005) and MDD PRS (p=0.009) predict poorer response; BD-PRS not predictive. SCZ+MDD (MET2) PRS improves prediction (partial R^2=0.91%). Top MET2 decile OR=2.54 for poor response.	Combining SCZ and MDD PRS refines lithium response prediction.
Cearns et al, 2022 [47]	PRS and clinical data for lithium response	Multimodal ML approach, cross-validation	Lithium (long-term)	BD=1034	Unimodal PRS ≤2% variance; combined clinical+PRS ≤7.4%. Stratifying by SCZ+MDD PRS improves to 13.7%. Lowest meta-PRS quartile OR=1.677 (p=0.009) for better response vs highest quartile.	PRS plus clinical data improve prediction.
Grigoroiu-Serbanescu et al, 2024 [48]	SCZ PRS and BP-I traits	Cross-sectional	No active treatment (observational)	BP-I=1878 (574 RO, 1304 UK), Controls=2751 (534 RO, 2217 UK)	SCZ PRS predicts earlier onset (depression AO β=-1.2, p=1.96E-04; mania AO β=-1.34, p=4.82E-05), psychosis (OR=1.589, p=1.53E-42), less rapid cycling (OR=0.637, p=2.13E-09). PRS+clinical improves psychosis AUC=0.785.	Integrating SCZ PRS with clinical data improves BP-I trait prediction.
Song et al, 2024 [49]	PRS and BD subphenotypes	Cross-sectional, meta-analytic	No active treatment (observational)	BD=5180 (Sweden), BD=2577 (UK)	SCZ PRS reduces inter-episode remission (OR=0.91, p=6.98×10^{-4}), increases psychotic symptoms (OR=1.19, p=2.07×10^{-8}), trends toward lower functioning (β=-0.49, p=0.01).	SCZ PRS may influence BD psychosis and remission.

Abbreviation: AO, Age of Onset; AUC, Area Under the Curve; BD, Bipolar Disorder; GAF, Global Assessment of Functioning; HLA, Human Leukocyte Antigen; MDD, Major Depressive Disorder; ML, Machine Learning; SCZ PRS, Schizophrenia Polygenic Risk Score.

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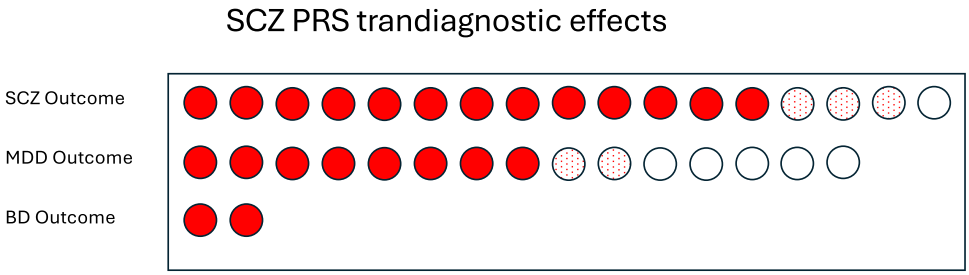

Figure 1 Visual summary, circles indicate independent studies. Full circle: positive or nominal association, dotted circle: consistent trend, empty circle: no association.

Beyond treatment response, SCZ PRS is also associated with key clinical features and phenotypic dimensions that transcend diagnoses such as age of onset, psychosis incidence, rapid cycling, psychotic features, and inter-episode remission in BD, although this was not the primary aim of this review.

Moreover, environmental factors, such as childhood adversity or frequent cannabis use, also appear to modulate the relationship between SCZ PRS and clinical outcomes, as suggested by urbanicity and environmental exposure studies.

In addition, several studies have indicated that SCZ PRS correlates with cognitive deficits, educational attainment, and related neurodevelopmental features.

However, not all studies were concordant, which may be explained by many factors including sample size, sample recruitment strategies, and confounding factors. Among the confounding factors, it is important to emphasize that the most recent SCZ PRS should be considered a more valid tool. In fact, the results of schizophrenia GWAS studies improved significantly between the Psychiatric Genomics Consortium 2 (PGC2) study in 2014,[24] which has been used in the majority of the reviewed studies, and the PGC3 study in 2022.[3] The PGC2 study identified 108 loci associated with schizophrenia using a sample of approximately 36,989 cases and 113,075 controls. By 2022, the PGC3 study had expanded the sample size substantially to 76,755 cases and 243,649 controls, enabling the identification of 287 genetic loci associated with schizophrenia. This increase in sample size led to greater statistical power, improved resolution in identifying risk variants, and enhanced the predictive power of the SCZ PRS across multiple phenotypes. Moreover, other possible limitations are still present before a broad application of SCZ PRS in routine clinical practice. Being SCZ PRS summarized in a single numerical value, it has the potential to easily classify patients at high or low risk and therefore guide treatment,[2,7,53] however before that we need to reach a solid and unequivocal scientific evidence and knowledge of potential ethnic variations.[54] In particular many of the reviewed studies had a cross sectional design, thus not allowing causal inference. In order to reach a more complete landscape of SCZ PRS effects we need adequately powered prospective studies.

Overall, cumulative evidence demonstrates that the SCZ PRS acts as a potential transdiagnostic marker of severity and poor outcome, particularly if combined with multimodal approaches. The transdiagnostic utility of the SCZ PRS lies in its potential to identify individuals who may require more intensive or alternative treatment strategies, earlier interventions, or targeted approaches to improve the outcomes.[55–58]

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