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Schizophrenia Genetics Modulates Clinical Depressive Features

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ABSTRACT

Schizophrenia (SCZ) genetic liability, quantified by polygenic scores (PGS), may influence clinical phenotypes in major depressive disorder (MDD). We investigated the effect of the SCZ-PGS derived from the latest SCZ genome-wide association study (GWAS) on MDD symptom severity, comorbidities, and treatment outcomes. The study included 1060 adults diagnosed with MDD from the GSRD sample, with replication in the STAR*D sample ($n = 1503$ MDD). Baseline and current depressive symptoms were assessed along with functional impairment and comorbid conditions. SCZ-PGS was calculated based on the latest SCZ GWAS summary statistics. Higher SCZ-PGS was associated with more severe baseline depressive symptoms, including apparent sadness, inner tension, lassitude, pessimistic thoughts, and suicidality. Functional impairment in social, familial, and work domains also increased with higher SCZ-PGS. Multivariable models suggested a small but significant independent association between elevated SCZ-PGS and poorer outcomes, confirmed in the STAR*D sample. Elevated SCZ-PGS correlated with a series of features suggesting more severe depression in both samples. Our findings confirm that the latest SCZ genetic liability scores contribute to MDD clinical heterogeneity, increasing depressive severity, functional impairment, and anxiety comorbidity. Although its influence on treatment response appears modest, SCZ-PGS may serve as a marker for more severe depressive presentations.

1 | Introduction

Major depressive disorder (MDD) is a highly prevalent and disabling condition characterized by a diverse clinical presentation, including marked variability in symptom profiles, illness course, and response to treatment (Bartova et al. 2019; Chen et al. 2024; Fried and Nesse 2015; Proudman et al. 2021; Tsigkaropoulou et al. 2023). Although a range of pharmacological and psychosocial interventions exists, a substantial proportion of patients fail to achieve adequate remission with first-line therapies (McIntyre et al. 2023; Sforzini et al. 2022). This treatment outcome heterogeneity is likely linked to biological markers that could predict clinical variability and guide personalized treatment strategies (Pain et al. 2022). Recent studies have revealed the complex polygenic architecture of MDD, with genome-wide association studies (GWAS) implicating hundreds of common variants in disease susceptibility (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium 2025). Moreover, MDD shares considerable genetic overlap with other psychiatric disorders, most notably schizophrenia, with an estimated genetic correlation of approximately 0.3 between schizophrenia (SCZ) and MDD (Grotzinger et al. 2022). SCZ itself is characterized by a highly polygenic background, with numerous risk loci contributing to its pathogenesis (Trubetskoy et al. 2022).

Polygenic scores (PGS) have emerged as a powerful tool to quantify an individual's genetic liability by aggregating the effects of common variants (i.e., single nucleotide polymorphisms—SNPs). Although originally developed to estimate risk for a given disorder, PGS have increasingly been employed to explore cross-disorder influences on clinical phenotypes (Fanelli, Sokolowski, et al. 2022), including brain structures (Cattarinussi et al. 2022), though their clinical utility is still debated (Koch et al. 2023; Sharew et al. 2024).

Recent evidence suggests that SCZ-PGS may influence clinical features in MDD (Whalley et al. 2016). Patients with depression who carry a higher burden of SCZ risk alleles might show distinct symptom profiles or a more severe clinical course. More interestingly, preliminary findings suggest a potential relationship between elevated SCZ-PGS and reduced responsiveness to antidepressant treatments (Fanelli, Domschke, et al. 2022; Fanelli et al. 2021; Li et al. 2020; Meerman et al. 2022; Oliva et al. 2023; Wigmore et al. 2020), though not unequivocally (Elsheikh et al. 2024; García-González et al. 2017), and also with reduced responsiveness to lithium in bipolar disorder (International Consortium on Lithium Genetics (ConLi+Gen) et al. 2018; Serretti and Baune 2025).

These observations raise the possibility that SCZ-PGS could serve as a biomarker for identifying MDD patients at increased risk of a specific clinical profile or treatment resistance, thereby informing more targeted and effective therapeutic strategies. However, despite these promising studies, the influence of SCZ genetic liability on depression heterogeneity remains insufficiently characterized.

We previously investigated the present sample regarding antidepressant outcome, clinical features (Fanelli et al. 2021), and melancholic features (Oliva et al. 2023); however, results were based on the previous SCZ GWAS (Ripke et al. 2014), while the most recent SCZ GWAS expanded the identified loci from 108 to 287 with an explained variance of PGS of 7.3% and a SNP-based heritability of 24%, with an impressive odds ratio of 39 [95% confidence intervals: 29, 53] of the lowest compared to the highest SCZ-PGS centile, overall a more than double prediction compared to the previous GWAS (Trubetskoy et al. 2022). Moreover, the specific effect of SCZ-PGS on depressive symptomatology has not been investigated.

In light of this evidence, the present study aims to evaluate the effects of the most powerful SCZ-PGS, computed using the most recent SCZ GWAS summary statistics (Trubetskoy et al. 2022), on depression features and outcomes in a large, well-characterized cohort of individuals with MDD (Bartova et al. 2019) with a replication in an independent sample (Rush et al. 2004, 2006). By integrating the latest genomic data with detailed clinical phenotyping, we investigated the potential contribution of SCZ genetic liability to the clinical heterogeneity of depression.

2 | Methods

2.1 | Group for the Study of Resistant Depression Sample

Patients included in the present research were collected as part of the cross-sectional, naturalistic, multicenter European Group for the Study of Resistant Depression (GSRD) study. As detailed elsewhere (Bartova et al. 2019; Dold et al. 2016), adults with current MDD were diagnosed according to DSM IV-TR criteria; exclusion criteria included severe psychotic features, medical and substance abuse disorders that, in the opinion of the treating clinician, could impair the validity of the observations; participants were naturalistically treated with at least one antidepressant drug at a sufficient dose for at least 4 weeks. Demographic and clinical data were collected as previously reported (Dold et al. 2016; Panariello et al. 2023). The Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) was administered at inclusion and to assess retrospectively symptoms at the beginning of the current episode (considering patients' interviews and medical records). Patients were classified as responders if a reduction in total MADRS score $\geq$ 50% from baseline was obtained after $\geq$ 4 weeks of treatment; otherwise, they were considered non-responders. In case of non-response after two or more trials, patients were defined as TRD. Additional assessments included the Sheehan Disability Scale (SDS) (Sheehan 1983), Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998), Hamilton Depression Rating Scale (HAMD) (Hamilton 1967), Young Mania Rating Scale (YMRS) (Young et al. 1983), and the Committee of Clinical Investigations side effect scale (Lingjaerde et al. 1987). Clinical and demographic features were collected using MINI and clinical interviews. Out of the original sample of 1400 patients, after quality controls and genetic data availability, 1060 were included in the present paper. All procedures of this study comply with the Helsinki Declaration and were approved by the local ethics committees of each research centre involved in the study (coordinating centre approval number: B406201213479). Written

informed consent was provided by all patients included in this study.

2.2 | Sequenced Treatment Alternatives to Relieve Depression Sample

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) sample, a total of 4041 participants with MDD (DSM-IV criteria) were enrolled from primary care or psychiatric outpatient clinics. Of these, 2876 patients met the inclusion criterion of having at least moderate depression severity, and 1948 were genotyped. Severity of depression was assessed using the 16-item Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR16) (Trivedi et al. 2004) at baseline and every 2 weeks until week 12. In the present analysis, only data from level 1 were included, where all patients received citalopram (Rush et al. 2004, 2006). In the STAR*D sample, response was defined as QIDS-SR16 < 13 (equivalent to MADRS ≤ 22) and a ≥ 50% score reduction from baseline (Trivedi et al. 2004). Work and Social Adjustment Scale (WSAS) was used to evaluate the functional impairment (Mundt et al. 2002). Written informed consent was provided by all patients included in this study.

2.3 | Genotyping and Quality Control of the Target Datasets

Genome-wide genotyping in GSRD was performed using the Illumina Infinium PsychArray 24 BeadChip (Illumina Inc., San Diego) as previously reported (Oliva et al. 2023). In STAR*D, data were obtained using the Affymetrix Human Mapping 500 K Array Set or Affymetrix Genome-Wide Human SNP Array 5.0 (Affymetrix, South San Francisco, California). Briefly, SNPs and subjects were removed with a missing genotype rate ≥ 5%, monomorphic variants, genotyping rate < 97%, sex discrepancies, abnormal heterozygosity, population outliers (outside five standard deviations for the first 20 population principal components), or high relatedness (identity by descent (IBD) > 0.1875) (Anderson et al. 2010; Patterson et al. 2006) or if they were not of Caucasian ethnicity. Minimac3 and reference data from the Haplotype Reference Consortium (HRC) r1.1 2016 were used for imputation. Variants with minor allele frequency (MAF) < 0.01, poor imputation quality ($r^2 < 0.30$), and genotype probability < 0.90 were eliminated (Li et al. 2010).

2.4 | Statistical Analyses

SCZ-PGS were computed based on publicly available summary statistics of the largest and most recent GWAS on SCZ, including 76,755 individuals with schizophrenia and 243,649 controls. EUR summary statistics (52,017 cases and 75,889 controls) were used (Trubetskoy et al. 2022). All data were aligned to Genome Reference Consortium Human Build 37. Summary statistics were restricted to autosomal HapMap3 SNPs present in the 1000 Genomes EUR reference; duplicates and multi-allelic sites were removed, and strand-ambiguous A/T and C/G SNPs with MAF ≥ 0.40 were excluded. Variants with missing fields, INFO < 0.8, or MAF < 0.01 were filtered out. Linkage disequilibrium was modeled with the 1000 Genomes Phase 3 European HapMap3 LD reference. PGS calculation was performed using PRS-CS, a polygenic prediction method that infers posterior SNP effect sizes under continuous shrinkage, with a fixed global shrinkage parameter $\varphi = 1e{-}2$. We used the default CS prior hyperparameters ($a = 1$, $b = 0.5$) and Markov Chain Monte Carlo settings (1000 iterations; 500 burn-in; thinning = 5), estimating posterior SNP effects chromosome-wise (1–22). Individual-level scores were computed in PLINK v1.90 using the PRS-CS posterior betas and then z-standardized within the target sample prior to association analyses (Choi and O'Reilly 2019; Oliva et al. 2023; Pitharouli et al. 2021; Purcell et al. 2007; Wray et al. 2018). Standardized SCZ-PGS were used as independent variables in univariable and multivariable analyses, including previously reported predictors (age, number of depressive episodes, suicidal risk, anxiety disorders, working status, SDS social, antipsychotics, duration of disease, and number of previous antidepressants) (Bartova et al. 2019), adjusting for two population principal components. All analyses were performed using Python version 3 for MacOS and Jamovi (The Jamovi Project, jamovi (Version 2.6) [Computer Software] 2024; Virtanen et al. 2020). The statistical significance level was set at $p = 0.05$, uncorrected because of the confirmative nature of the analysis given the previously reported studies on SCZ-PGS and depression (Amrhein et al. 2019).

3 | Results

3.1 | GSRD Sample

A total of 1060 GSRD patients with MDD were included in the analysis. Tables 1 and 2 report the sample description and distribution of SCZ-PGS in continuous and categorical variables, respectively.

Overall, higher SCZ-PGS was associated with characteristics indicating more severe depression, including a higher baseline MADRS score (rho = 0.109; $p = 0.0003$) and specifically higher severity of apparent sadness, reported sadness, inner tension, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The distribution of baseline symptomatology profile across SCZ-PGS quintiles is shown in Figure 1.

SCZ-PGS was also correlated with all three domains of the SDS, that is, work, social, and family functioning, in the direction of a worse impact on functioning in all domains with increasing SCZ-PGS (Table 1).

Although SCZ-PGS was not associated with treatment outcome, a non-significant trend in the expected direction was observed. However, higher SCZ-PGS was associated with more severe current (after treatment) depressive symptoms, as indicated by MADRS (rho = 0.092; $p = 0.0026$), HAMD-17 (rho = 0.093; $p = 0.0025$), and overall MINI severity ($t = -2.458$, $p = 0.014$). The current MADRS symptom profile showed association patterns with SCZ-PGS similar to those observed when considering the baseline MADRS, suggesting a modulatory effect of SCZ-PGS independent from symptom improvement. The current, after treatment, HAMD profile association with SCZ-PGS was similar to the previously reported

TABLE 1 | Association of continuous clinical and socio-demographic variables with SCZ-PGS in the GSRD sample.

Variable	Mean (SD), *N*	Correlation (95% C.I.)	*p*
MADRS Outcome (1 responders, 2 non responders, 3 resistant)	2.16 (0.79), *N* = 1060	0.032 (−0.028–0.092)	0.292
HAMD Outcome (1 responders, 2 non responders, 3 resistant)	2.09 (0.84), *N* = 1060	0.042 (−0.018–0.102)	0.171
Age (years)	51.81 (13.77), *N* = 1058	−0.063 (−0.123–0.003)	**0.040**
MADRS Retrospective	34.39 (7.53), *N* = 1060	0.110 (0.05–0.169)	**< 0.001**
MADRS Current	24.72 (11.35), *N* = 1060	0.092 (0.032–0.151)	**0.003**
Education (years)	2.78 (0.95), *N* = 1052	−0.056 (−0.116–0.004)	0.068
Working status (1–4)	2.23 (1.31), *N* = 1055	−0.037 (−0.097–0.023)	0.225
Bmi	25.70 (5.42), *N* = 1058	0.004 (−0.056–0.064)	0.895
Sheehan Work	6.47 (2.87), *N* = 985	0.103 (0.041–0.164)	**0.001**
Sheehan Social	6.42 (2.66), *N* = 1050	0.108 (0.048–0.167)	**0.001**
Sheehan Family	6.14 (2.66), *N* = 1031	0.083 (0.022–0.143)	**0.008**
MADRS retrospective			
Apparent sadness MADRS retrospective	4.20 (1.05), *N* = 1051	0.066 (0.006–0.126)	**0.034**
Reported sadness MADRS retrospective	4.31 (0.97), *N* = 1051	0.070 (0.01–0.13)	**0.022**
Inner tension MADRS retrospective	3.57 (1.18), *N* = 1051	0.086 (0.026–0.146)	**0.005**
Reduced sleep MADRS retrospective	3.61 (1.42), *N* = 1051	0.018 (−0.043–0.078)	0.567
Reduced appetite MADRS retrospective	2.24 (1.71), *N* = 1051	0.039 (−0.022–0.099)	0.209
Concentration difficulties MADRS retrospective	3.55 (1.14), *N* = 1051	0.050 (−0.011–0.11)	0.103
Lassitude MADRS retrospective	3.85 (1.10), *N* = 1051	0.076 (0.016–0.136)	**0.014**
Inability-feel MADRS retrospective	3.60 (1.19), *N* = 1051	0.061 (0.001–0.121)	0.050
Pessimistic thoughts MADRS retrospective	3.45 (1.26), *N* = 1051	0.089 (0.029–0.149)	**0.004**
Suicidal thoughts MADRS retrospective	1.94 (1.73), *N* = 1051	0.067 (0.007–0.127)	**0.031**
HAMD Current			
Depressed mood HAMD Current	2.24 (1.06), *N* = 1060	0.076 (0.016–0.136)	**0.014**
Feelings of guilt HAMD Current	1.62 (1.06), *N* = 1060	0.102 (0.042–0.161)	**0.001**
Suicide HAMD Current	0.81 (1.05), *N* = 1060	0.039 (−0.021–0.099)	0.200
Insomnia-early HAMD Current	0.85 (0.84), *N* = 1060	0.004 (−0.056–0.064)	0.892
Insomnia-middle HAMD Current	0.98 (0.82), *N* = 1060	−0.033 (−0.093–0.027)	0.287
Insomnia-late HAMD Current	0.75 (0.80), *N* = 1060	0.004 (−0.056–0.064)	0.896
Work and Activities HAMD Current	2.31 (1.18), *N* = 1060	0.038 (−0.022–0.098)	0.219
Retardation HAMD Current	1.25 (1.01), *N* = 1060	0.098 (0.038–0.157)	**0.001**
Agitation HAMD Current	0.80 (0.94), *N* = 1060	0.035 (−0.025–0.095)	0.254
Anxiety-psychic HAMD Current	1.63 (1.04), *N* = 1060	0.091 (0.031–0.15)	**0.003**
Anxiety-somatic HAMD Current	1.47 (1.03), *N* = 1060	0.063 (0.003–0.123)	**0.042**
Somatic symptoms-gastrointestinal HAMD Current	0.70 (0.68), *N* = 1060	0.083 (0.023–0.143)	**0.007**
Somatic symptoms-general HAMD Current	0.97 (0.73), *N* = 1060	0.081 (0.021–0.141)	**0.008**

(Continues)

TABLE 1 | (Continued)

Variable	Mean (SD), *N*	Correlation (95% C.I.)	*p*
Genital symptoms HAMD Current	1.02 (0.85), *N* = 1060	0.040 (−0.02–0.1)	0.196
Hypochondriasis HAMD Current	0.98 (1.06), *N* = 1060	0.115 (0.055–0.174)	**< 0.001**
Loss of weight HAMD Current	0.38 (0.65), *N* = 1060	−0.029 (−0.089–0.031)	0.350
Insight HAMD Current	0.17 (0.42), *N* = 1060	0.024 (−0.036–0.084)	0.434
HAMD 17 Total	18.92 (8.71), *N* = 1060	0.093 (0.033–0.152)	**0.003**
Diurnal variation HAMD Current	0.61 (0.77), *N* = 1060	−0.065 (−0.125–0.005)	**0.034**
Diurnal variation Morning HAMD Current	1.07 (0.29), *N* = 292	0.027 (−0.088–0.141)	0.647
Diurnal variation Evening HAMD Current	1.74 (0.54), *N* = 108	−0.077 (−0.262–0.114)	0.427
Depersonalization and derealization HAMD Current	0.23 (0.58), *N* = 1060	−0.014 (−0.074–0.046)	0.646
Paranoid symptoms HAMD Current	0.13 (0.43), *N* = 1060	0.030 (−0.03–0.09)	0.337
Obsessional and Compulsive symptoms HAMD Current	0.12 (0.37), *N* = 1060	0.031 (−0.029–0.091)	0.318
HAMD 21 Total	19.98 (9.06), *N* = 1060	0.085 (0.025–0.144)	**0.006**
MADRS current			
Apparent sadness MADRS current	3.10 (1.55), *N* = 1060	0.080 (0.02–0.14)	**0.010**
Reported sadness MADRS current	3.17 (1.52), *N* = 1060	0.091 (0.031–0.15)	**0.003**
Inner tension MADRS current	2.53 (1.33), *N* = 1060	0.098 (0.038–0.157)	**0.002**
Reduced sleep MADRS current	2.52 (1.69), *N* = 1060	0.040 (−0.02–0.1)	0.189
Reduced appetite MADRS current	1.39 (1.53), *N* = 1060	0.023 (−0.037–0.083)	0.450
Concentration difficulties MADRS current	2.69 (1.39), *N* = 1060	0.091 (0.031–0.15)	**0.003**
Lassitude MADRS current	2.88 (1.48), *N* = 1060	0.101 (0.041–0.16)	**0.001**
Inability-feel MADRS current	2.59 (1.53), *N* = 1060	0.060 (−0.0–0.12)	0.053
Pessimistic thoughts MADRS current	2.65 (1.46), *N* = 1060	0.081 (0.021–0.141)	**0.008**
Suicidal thoughts MADRS current	1.27 (1.43), *N* = 1060	0.045 (−0.015–0.105)	0.144
Young Current			
Elevated mood Young Current	0.04 (0.24), *N* = 1060	−0.004 (−0.064–0.056)	0.885
Increased motor activity-energy Young Current	0.06 (0.32), *N* = 1060	−0.035 (−0.095–0.025)	0.258
Sexual interest Young Current	0.02 (0.21), *N* = 1060	−0.020 (−0.08–0.04)	0.517
Sleep Young Current	0.50 (0.85), *N* = 1060	0.018 (−0.042–0.078)	0.556
Irritability Young Current	0.54 (1.13), *N* = 1060	−0.019 (−0.079–0.041)	0.545
Speech Young Current	0.09 (0.51), *N* = 1060	0.003 (−0.057–0.063)	0.927
Language-Thought disorder Young Current	0.05 (0.26), *N* = 1060	0.012 (−0.048–0.072)	0.708
Content Young Current	0.04 (0.34), *N* = 1060	0.023 (−0.037–0.083)	0.454
Disruptive-Aggressive behavior Young Current	0.05 (0.38), *N* = 1060	0.003 (−0.057–0.063)	0.918
Appearance Young Current	0.09 (0.36), *N* = 1060	0.008 (−0.052–0.068)	0.789
Insight Young Current	0.05 (0.25), *N* = 1060	−0.026 (−0.086–0.034)	0.400
Young Current Total	1.53 (2.60), *N* = 1060	−0.005 (−0.065–0.055)	0.881
Clinical features			
Duration Episode MINI	215.68 (189.37), *N* = 919	−0.004 (−0.069–0.061)	0.915

(Continues)

TABLE 1 | (Continued)

Variable	Mean (SD), *N*	Correlation (95% C.I.)	*p*
Number of Depressive Episodes	3.59 (2.59), *N* = 824	0.113 (0.045–0.18)	**0.001**
Age at Onset (years)	36.92 (15.06), *N* = 1006	−0.058 (−0.119–0.004)	0.067
Duration of Disease (years)	14.98 (12.94), *N* = 997	0.010 (−0.052–0.072)	0.762
Age of the last Episode (years)	47.86 (13.50), *N* = 1028	−0.058 (−0.119–0.003)	0.062
Time of hospitalizations	5.28 (17.05), *N* = 1002	0.034 (−0.028–0.096)	0.279
Age at first hospitalization (years)	44.63 (15.13), *N* = 394	−0.029 (−0.127–0.07)	0.563
Suicidal Risk	0.89 (1.09), *N* = 1059	0.049 (−0.011–0.109)	0.114
Psychiatric side effects log	0.59 (0.45), *N* = 1059	0.014 (−0.046–0.074)	0.655
Neurologic side effects log	0.12 (0.22), *N* = 1059	−0.026 (−0.086–0.034)	0.390
Autonomic side effects log	0.29 (0.30), *N* = 1059	−0.017 (−0.077–0.043)	0.571
Other side effects log	0.34 (0.36), *N* = 1059	−0.035 (−0.095–0.025)	0.263
Side Effects Total log	1.03 (0.29), *N* = 1059	−0.009 (−0.069–0.051)	0.779
Number of previous antidepressants	1.52 (1.61), *N* = 1059	−0.033 (−0.093–0.027)	0.291
Antidepressant dose equivalents Total	45.38 (25.37), *N* = 972	0.080 (0.017–0.142)	**0.013**

Note: Univariable analysis. Nominal significant findings are reported in bold.

MADRS retrospective one (Table 1). We confirmed with this new SCZ-PGS the previously reported positive association with the number of previous depressive episodes (rho = 0.113; $p = 0.0011$) (Fanelli et al. 2021). However, SCZ-PGS was not associated with age at onset, duration of disease, or number of hospitalizations (Table 1). No association was observed for the side effect profile, not investigated in the previous report, but a mild association was observed with the antidepressant dose equivalent (Table 1) and with the use of antipsychotics augmentation ($t = -2.292$; $p = 0.022$) (Table 2).

Comorbidities with anxiety disorders, including panic disorder and generalized anxiety disorders, were associated with higher SCZ-PGS (Table 2), in a more significant way compared to the previous report (Fanelli et al. 2021). SCZ-PGS were also associated with psychotic features during the current episode and, as a trend as in the previous report, lifetime psychotic features (Table 2). A trend of association with a family history of bipolar disorder was also observed, as expected given the genetic correlation between SCZ and bipolar disorder, which was not observed in the previous report.

Finally, we replicated the previous finding of a different outcome of antipsychotic augmentation depending on SCZ-PGS (Fanelli et al. 2021), with patients with higher SCZ-PGS showing higher benefit from antipsychotic augmentation (response rate by high vs. low SCZ-PGS, chi-square = 5.34; $p = 0.021$) and the opposite in lower SCZ-PGS.

In the multivariable model, adding as covariates the factors previously associated with treatment resistance (age, number of depressive episodes, suicidal risk, anxiety disorders, working status, SDS social, antipsychotics, duration of disease, and number of previous antidepressants), SCZ-PGS was nominally associated with treatment outcome ($F = 2.804$, $p = 0.025$) but with a pseudo R2 variance explained of only 1.2%.

Given that GSRD patients were more severe at baseline (MADRS = 34.39 vs. HAMD = 19.46), we repeated the analyses after matching severity (MADRS = 26 equal HAMD = 20) (Leucht et al. 2018). This reduced the sample size to 302 and, as expected, the sample size reduction led to less significant findings; however, correlation coefficients and mean differences were very similar to the original sample (Tables S1 and S2).

3.2 | STAR*D Sample

In the STAR*D sample (1503 subjects analyzed), SCZ-PGS was not associated with overall baseline severity measured with HAMD or QIDS-SR, though with non-significant trends in the same direction as the GSRD sample. However, we confirmed the association of SCZ-PGS with depressed mood (QIDS), anxiety (HAMD), and lassitude (both HAMD energy and QIDS retardation), while the other symptoms were not confirmed (Table 3). Other symptoms showed significant SCZ-PGS effects in both HAMD and QIDS but without corresponding effects on GSRD MADRS or in the opposite direction, and were partially similar after treatment, with the exception of suicidal ideation (Table 3). However, the percent improvement in HAMD was associated with SCZ-PGS (rho = −0.075; $p = 0.008$), with a trend in the same direction for QIDS (rho = −0.048; $p = 0.068$). The association between functional impairment and SCZ-PGS was replicated in the STAR*D using the WSAS (Table 3).

In the STAR*D sample, higher SCZ-PGS was associated with greater severity of both insomnia and hypersomnia symptoms

TABLE 2 | Association of categorical clinical and socio-demographic variables with SCZ-PGS in the GSRD sample.

Variable (No/Yes)	PRS SCZ Mean (SD), *N*	PRS SCZ Mean (SD), *N*	*T*-test	*p*
Sex (M/F)	0.074 (0.927), 359	−0.036 (0.902), 699	1.839	0.066
Married	0.012 (0.919), 540	−0.012 (0.905), 520	0.426	0.670
Living with others	−0.007 (0.941), 350	0.003 (0.898), 710	−0.167	0.867
Children	0.062 (0.847), 361	−0.032 (0.942), 699	1.656	0.098
Smoking	−0.061 (0.892), 520	0.075 (0.929), 514	−2.401	0.017
Family history MDD	0.024 (0.920), 680	−0.045 (0.899), 378	1.189	0.235
Family history BD	−0.012 (0.914), 1009	0.236 (0.844), 49	−2.002	0.050
Family history suicide	0.010 (0.906), 982	−0.131 (0.975), 78	1.243	0.217
Thyroid Disorder	−0.011 (0.908), 901	0.052 (0.934), 152	−0.775	0.439
Diabetes	0.005 (0.913), 989	−0.107 (0.895), 64	0.969	0.336
Psychotherapy	0.008 (0.898), 642	−0.064 (0.922), 317	1.147	0.252
Severity MINI	−0.087 (0.896), 435	0.057 (0.922), 529	−2.458	**0.014**
Psychotic Lifetime	−0.007 (0.918), 698	0.279 (1.029), 46	−1.839	0.072
Psychotic Current	−0.008 (0.917), 695	0.320 (1.081), 50	−2.097	**0.041**
Chronicity	−0.013 (0.927), 868	0.072 (0.830), 185	−1.245	0.214
Inpatient	−0.046 (0.893), 686	0.090 (0.938), 367	−2.281	**0.023**
Dysthymia	−0.000 (0.912), 1051	0.130 (1.108), 6	−0.287	0.786
OCD	−0.004 (0.911), 1035	0.256 (0.901), 15	−1.109	0.286
PTSD	−0.005 (0.914), 1042	0.345 (0.715), 17	−1.993	0.063
Panic Disorder	−0.023 (0.914), 958	0.220 (0.865), 101	−2.664	**0.009**
GAD	−0.025 (0.906), 946	0.211 (0.937), 113	−2.54	**0.012**
Mood Stabilizers	−0.013 (0.914), 928	0.086 (0.896), 131	−1.182	0.239
Antipsychotics	−0.044 (0.896), 736	0.098 (0.942), 323	−2.292	**0.022**
Benzodiazepines	−0.006 (0.904), 707	0.010 (0.930), 352	−0.267	0.790
Somatic disorders	−0.009 (0.911), 465	0.006 (0.914), 594	−0.254	0.800
SSRI	0.054 (0.901), 474	−0.044 (0.919), 585	1.744	0.082
SNRI	−0.002 (0.914), 883	0.007 (0.905), 176	−0.127	0.899
NRI	0.000 (0.913), 1056	−0.267 (0.795), 3	0.582	0.619
TCA	−0.000 (0.905), 975	−0.005 (0.994), 84	0.047	0.963
NDRI	−0.000 (0.917), 1020	−0.002 (0.781), 39	0.015	0.989
NASSA	−0.009 (0.890), 886	0.045 (1.019), 173	−0.652	0.515
MAOI	−0.003 (0.911), 1055	0.644 (1.133), 4	−1.14	0.337
SARI	−0.002 (0.912), 937	0.009 (0.919), 122	−0.127	0.899
Other AD	−0.009 (0.921), 845	0.033 (0.879), 214	−0.627	0.531
Combination treatment	0.002 (0.886), 738	−0.006 (0.970), 321	0.122	0.903

Note: Univariable analysis. Nominal significant findings are reported in bold.

as measured by the QIDS-SR (Table 3). Although these associations did not reach statistical significance in the GSRD cohort, a consistent directionality across both datasets was found.

Other potentially interesting findings in the STAR*D were the association of SCZ-PGS with lower education and no family history of MDD (in both samples in the same direction, though

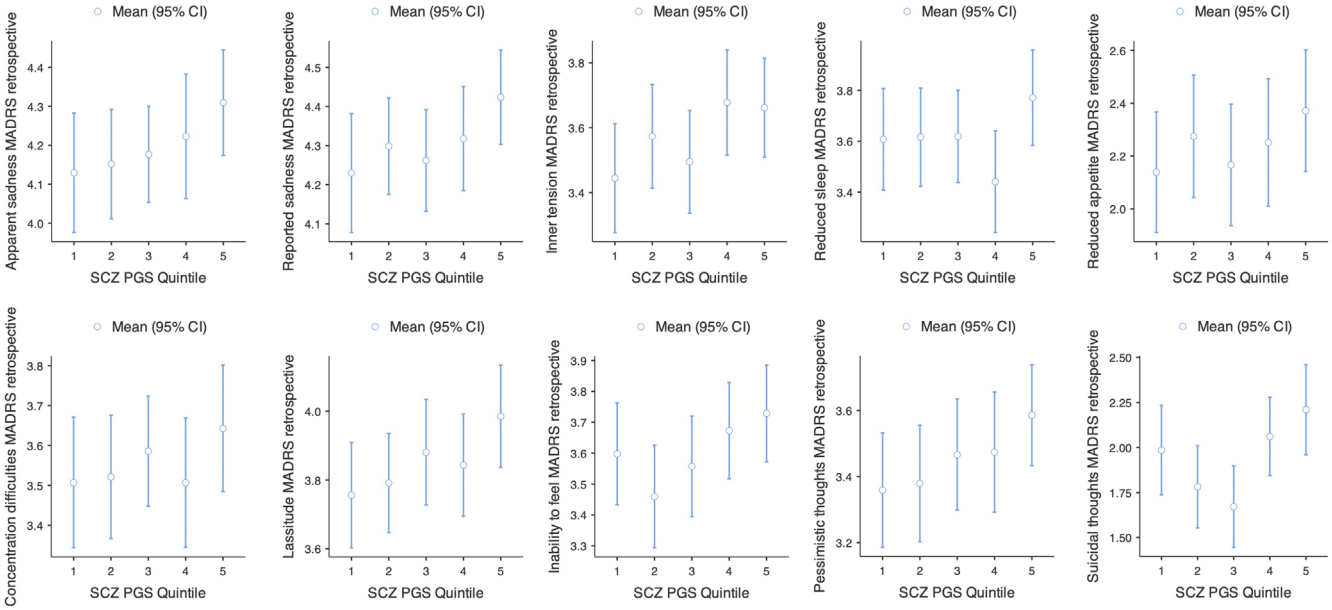

FIGURE 1 | Distribution of baseline symptomatology profile across SCZ-PGS quintiles.

not statistically significant in GSRD), and the association with insomnia that, however, was not observed in the GSRD, though coefficients were in the same direction (Tables 1–4).

4 | Discussion

Samples were described in previous publications, and the distribution of clinical and socio-demographic features is reported in Tables 1–4. In the large, naturalistically treated GSRD sample of European patients with MDD, we found that higher SCZ-PGS was associated with a more severe depressive presentation across multiple clinical domains. Specifically, elevated SCZ-PGS correlated with higher baseline symptom severity. This association was mirrored at follow-up, suggesting that the observed influence of SCZ genetic liability on depressive severity endures beyond initial treatment. Higher SCZ-PGS was also linked to worse functional impairment, also in the replication sample, suggesting a broader impact on social, familial, and work-related domains. In the replication sample, only a few symptoms were replicated; however, the direction of the effect was consistent across multiple results (summarized in Figure 2).

Our findings expand on prior reports suggesting that SCZ genetic liability contributes to the heterogeneity of MDD (Fanelli, Domschke, et al. 2022; Fanelli et al. 2021; Li et al. 2020; Meerman et al. 2022; Oliva et al. 2023; Whalley et al. 2016; Wigmore et al. 2020). By using the latest and most powerful SCZ GWAS summary statistics available (Trubetskoy et al. 2022)—which capture a considerably larger set of risk variants than earlier data sets—we provide a more refined estimate of SCZ genetic effects on depressive phenotypes. Our results confirm the finding that patients with MDD bearing a higher load of SCZ risk alleles not only report more severe depressive symptoms but also exhibit a broad detrimental effect on the depressive clinical presentation. Taken together, these findings suggest that SCZ-PGS may define a more severe subtype of MDD, in line with evidence of its transdiagnostic detrimental effects on a range of features (Serretti and Baune 2025).

Although we did not find a robust effect of higher SCZ-PGS on short-term treatment nonresponse, there was a modest trend in that direction. Of note, a multivariable model controlling for other established predictors of nonresponse (e.g., number of depressive episodes, suicidal risk, anxiety disorders, and social functioning) suggested that SCZ-PGS retained a small but significant association with the outcome. This is consistent with previous reports suggesting that higher SCZ-PGS may predispose patients to poorer antidepressant response (Fanelli, Domschke, et al. 2022; Fanelli et al. 2021; Li et al. 2020; Meerman et al. 2022). In the replication STAR*D sample, the effect on outcome was more evident across both HAMD and QIDS-SR outcomes. However, the effect sizes remained modest, indicating that SCZ genetic liability is only one factor within a broader set of influences shaping treatment trajectories in MDD.

Interestingly, our data confirm that patients with higher SCZ-PGS were more likely to receive and benefit from antipsychotic augmentation. This could reflect a clinical perception of greater severity or complexity in these patients' depressive presentations, particularly the presence of psychotic features, or might be indicative of clinicians' attempts to manage comorbid anxiety, agitation, or resistant symptoms (Huhn et al. 2019; Munayco Maldonado and Schwartz 2024; Ricci et al. 2025; Serretti 2024). Taken together, these patterns support the view that SCZ genetic load exerts a transdiagnostic influence that shapes MDD symptomatology and treatment choices, confirming our previous report (Fanelli et al. 2021).

Our findings broaden the understanding of sleep-related phenotypes in MDD by revealing a dual pattern of dysregulation. In STAR*D, elevated SCZ-PGS was linked to both increased insomnia and hypersomnia severity, reinforcing the hypothesis that schizophrenia-related genetic liability extends to sleep–wake regulation (O'Connell et al. 2021). Although this

TABLE 3 | Association of continuous clinical and socio-demographic variables with SCZ-PGS in the STAR*D sample.

Variable	Mean (SD), *N*	Correlation (95% C.I.)	*p*
School (years)	13.69 (3.34), *N* = 1500	−0.239 (−0.286–0.191)	**< 0.001**
Age first MD episode (y)	25.78 (14.82), *N* = 1491	0.029 (−0.022–0.08)	0.264
Age current episode (y)	43.04 (13.48), *N* = 1503	−0.026 (−0.076–0.025)	0.311
Disease duration (y)	17.25 (14.04), *N* = 1491	−0.055 (−0.105–0.004)	**0.033**
Number of episodes	5.79 (10.39), *N* = 1301	−0.047 (−0.101–0.007)	0.092
Episode duration (days)	740.19 (1617.81), *N* = 1492	−0.074 (−0.124–0.023)	**0.004**
WSAS	23.0 (9.04), *N* = 1121	0.118 (0.06–0.175)	**< 0.001**
HAMD initial insomnia Baseline	1.17 (0.91), *N* = 1441	0.071 (0.019–0.122)	**0.007**
HAMD middle insomnia Baseline	1.19 (0.86), *N* = 1438	0.021 (−0.031–0.073)	0.421
HAMD delayed insomnia Baseline	0.88 (0.90), *N* = 1440	0.017 (−0.035–0.069)	0.511
HAMD depressed mood Baseline	2.33 (0.90), *N* = 1440	−0.059 (−0.11–0.007)	**0.024**
HAMD psychic anxiety Baseline	1.66 (0.95), *N* = 1441	0.056 (0.004–0.107)	**0.033**
HAMD appetite Baseline	0.64 (0.82), *N* = 1440	0.003 (−0.049–0.055)	0.905
HAMD weight loss Baseline	0.36 (0.65), *N* = 1438	0.016 (−0.036–0.068)	0.555
HAMD guilt Baseline	1.83 (1.05), *N* = 1440	−0.036 (−0.087–0.016)	0.177
HAMD suicide Baseline	0.74 (0.88), *N* = 1440	−0.046 (−0.097–0.006)	0.081
HAMD interests Baseline	2.32 (1.04), *N* = 1441	−0.052 (−0.103–0.0)	**0.049**
HAMD somatic energy Baseline	1.42 (0.74), *N* = 1441	0.019 (−0.033–0.071)	0.464
HAMD libido Baseline	1.13 (0.90), *N* = 1441	−0.035 (−0.086–0.017)	0.182
HAMD retardation Baseline	0.53 (0.62), *N* = 1441	0.052 (0.0–0.103)	**0.049**
HAMD agitation Baseline	0.91 (0.86), *N* = 1441	−0.060 (−0.111–0.008)	**0.022**
HAMD somatic anxiety Baseline	1.64 (0.90), *N* = 1440	0.051 (−0.001–0.102)	0.052
HAMD hypocondria Baseline	0.70 (0.87), *N* = 1441	0.120 (0.069–0.171)	**< 0.001**
HAMD loss of insight Baseline	0.03 (0.21), *N* = 1441	0.018 (−0.034–0.07)	0.485
HAMD total Baseline	19.46 (6.43), *N* = 1441	0.017 (−0.035–0.069)	0.526
HAMD initial insomnia Final	0.68 (0.88), *N* = 1273	0.088 (0.033–0.142)	**0.002**
HAMD middle insomnia Final	0.73 (0.83), *N* = 1273	0.014 (−0.041–0.069)	0.622
HAMD delayed insomnia Final	0.51 (0.81), *N* = 1271	0.041 (−0.014–0.096)	0.145
HAMD depressed mood Final	0.98 (1.08), *N* = 1273	0.026 (−0.029–0.081)	0.359
HAMD psychic anxiety Final	0.88 (0.93), *N* = 1273	0.052 (−0.003–0.107)	0.062
HAMD appetite Final	0.27 (0.60), *N* = 1271	−0.027 (−0.082–0.028)	0.330
HAMD weight loss Final	0.21 (0.51), *N* = 1270	0.016 (−0.039–0.071)	0.580
HAMD guilt Final	0.90 (1.11), *N* = 1273	0.013 (−0.042–0.068)	0.645
HAMD suicide Final	0.30 (0.64), *N* = 1273	−0.038 (−0.093–0.017)	0.173
HAMD interests Final	1.25 (1.27), *N* = 1272	0.045 (−0.01–0.1)	0.106
HAMD somatic energy Final	0.82 (0.84), *N* = 1272	0.060 (0.005–0.115)	**0.033**
HAMD libido Final	0.75 (0.90), *N* = 1272	0.016 (−0.039–0.071)	0.564
HAMD retardation Final	0.27 (0.50), *N* = 1273	0.050 (−0.005–0.105)	0.075

(Continues)

TABLE 3 | (Continued)

Variable	Mean (SD), *N*	Correlation (95% C.I.)	*p*
HAMD agitation Final	0.59 (0.78), *N* = 1272	−0.011 (−0.066–0.044)	0.704
HAMD somatic anxiety Final	1.27 (0.96), *N* = 1273	0.066 (0.011–0.121)	0.019
HAMD hypocondria Final	0.47 (0.75), *N* = 1273	0.112 (0.057–0.166)	**< 0.001**
HAMD loss of insight Final	0.05 (0.31), *N* = 1273	−0.002 (−0.057–0.053)	0.948
HAMD total Final	10.92 (8.18), *N* = 1273	0.057 (0.002–0.112)	**0.042**
QIDS sleep onset insomnia QS0	1.61 (1.18), *N* = 1500	0.095 (0.045–0.145)	**< 0.001**
QIDS mid-nocturnal insomnia QS0	2.05 (1.04), *N* = 1500	0.015 (−0.036–0.066)	0.568
QIDS early morning insomnia QS0	1.26 (1.24), *N* = 1500	0.105 (0.055–0.155)	**< 0.001**
QIDS hypersomnia QS0	0.50 (0.83), *N* = 1500	−0.021 (−0.072–0.03)	0.421
QIDS mood (sad) QS0	2.10 (0.80), *N* = 1500	0.054 (0.003–0.104)	**0.035**
QIDS appetite (decreased) QS0	1.02 (0.87), *N* = 983	0.002 (−0.061–0.065)	0.943
QIDS appetite (increased) QS0	1.47 (1.04), *N* = 517	0.051 (−0.035–0.137)	0.252
QIDS weight (decrease) 2w QS0	1.05 (1.16), *N* = 924	0.061 (−0.004–0.125)	0.064
QIDS weight (increase) 2w QS0	1.57 (1.11), *N* = 576	0.027 (−0.055–0.108)	0.519
QIDS concentration/decision-making QS0	1.59 (0.79), *N* = 1499	0.029 (−0.022–0.08)	0.262
QIDS outlook (self) QS0	1.63 (1.10), *N* = 1499	0.019 (−0.032–0.07)	0.462
QIDS suicidal ideation QS0	0.66 (0.74), *N* = 1499	−0.059 (−0.109–0.008)	**0.024**
QIDS involvement QS0	1.77 (0.96), *N* = 1499	−0.115 (−0.165–0.065)	**< 0.001**
QIDS energy/fatigabilityQS0	1.71 (0.83), *N* = 1499	−0.015 (−0.066–0.036)	0.559
QIDS psychomotor slowing QS0	1.08 (0.81), *N* = 1499	0.071 (0.02–0.121)	**0.006**
QIDS psychomotor agitation QS0	1.10 (0.97), *N* = 1499	0.012 (−0.039–0.063)	0.651
QIDS total score (self) QS0	15.12 (4.29), *N* = 1499	0.014 (−0.037–0.065)	0.590
QIDS sleep onset insomnia QS12	0.75 (0.99), *N* = 738	−0.013 (−0.085–0.059)	0.729
QIDS mid-nocturnal insomnia QS12	1.49 (1.05), *N* = 738	−0.024 (−0.096–0.048)	0.516
QIDS early morning insomnia QS12	0.53 (0.93), *N* = 738	0.032 (−0.04–0.104)	0.379
QIDS hypersomnia QS12	0.44 (0.70), *N* = 738	−0.088 (−0.159–0.016)	0.017
QIDS mood (sad) QS12	0.73 (0.82), *N* = 738	−0.020 (−0.092–0.052)	0.596
QIDS appetite (decreased) QS12	0.30 (0.57), *N* = 532	−0.040 (−0.125–0.045)	0.355
QIDS appetite (increased) QS12	1.00 (0.85), *N* = 206	0.053 (−0.084–0.188)	0.447
QIDS weight (decrease) 2w QS12	0.37 (0.78), *N* = 500	0.033 (−0.055–0.12)	0.464
QIDS weight (increase) 2w QS12	1.23 (0.97), *N* = 238	0.090 (−0.038–0.215)	0.164
QIDS concentration/decision-making QS12	0.68 (0.74), *N* = 738	0.032 (−0.04–0.104)	0.392
QIDS outlook (self) QS12	0.50 (0.88), *N* = 738	−0.032 (−0.104–0.04)	0.389
QIDS suicidal ideation QS12	0.19 (0.50), *N* = 738	−0.078 (−0.149–0.006)	**0.035**
QIDS involvement QS12	0.61 (0.82), *N* = 738	0.022 (−0.05–0.094)	0.557
QIDS energy/fatigabilityQS12	0.74 (0.81), *N* = 738	0.046 (−0.026–0.118)	0.216
QIDS psychomotor slowing QS12	0.36 (0.64), *N* = 738	0.071 (−0.001–0.142)	0.055
QIDS psychomotor agitation QS12	0.56 (0.80), *N* = 738	0.002 (−0.07–0.074)	0.949

(Continues)

TABLE 3 | (Continued)

Variable	Mean (SD), *N*	Correlation (95% C.I.)	*p*
QIDS Final	8.07 (5.48), *N* = 1464	0.023 (−0.028–0.074)	0.375
Delta QIDS	7.06 (5.55), *N* = 1464	−0.011 (−0.062–0.04)	0.669
Percentage QIDS	45.86 (34.99), *N* = 1464	−0.048 (−0.099–0.003)	0.068
Delta HAMD	8.50 (7.91), *N* = 1227	−0.040 (−0.096–0.016)	0.160
Percentage HAMD	42.78 (43.12), *N* = 1227	−0.076 (−0.131–0.02)	**0.008**

Note: QS0 = Baseline, QS12 = 12th week. Univariable analysis Nominal significant findings are reported in bold.

TABLE 4 | Association of categorical clinical and socio-demographic variables with SCZ-PGS in the STAR*D sample.

Variable (no/yes)	PRS SCZ Mean (SD), *N*	PRS SCZ Mean (SD), *N*	*T*-test	*p*
Married	0.037 (0.984), 829	−0.045 (1.019), 674	−1.578	0.115
Employment	0.104 (1.081), 625	−0.074 (0.933), 878	−3.315	**< 0.001**
Sex (M/F)	−0.082 (0.897), 598	0.054 (1.060), 905	−2.689	**0.007**
Panic w/agoraphobia	0.038 (1.017), 1115	0.195 (1.119), 35	−0.818	0.419
Panic w/o agoraphobia	0.043 (1.025), 1114	0.020 (0.881), 36	0.154	0.878
Specific phobia	0.045 (1.019), 1139	−0.228 (1.128), 11	0.799	0.443
Social phobia	0.036 (1.012), 1083	0.142 (1.156), 67	−0.732	0.467
Obsessive compulsive disorder	0.044 (1.021), 1138	−0.104 (0.949), 12	0.538	0.601
Post-traumatic disorder	0.046 (1.023), 1078	−0.014 (0.982), 72	0.502	0.617
Generalized anxiety disorder	0.050 (1.033), 1068	−0.050 (0.829), 82	1.025	0.308
Family history of depression	0.093 (1.101), 632	−0.067 (0.914), 857	−2.986	**0.003**
Family history of bipolar	0.015 (1.018), 1351	−0.126 (0.805), 136	1.902	0.059
Responders QIDS	0.005 (0.955), 701	−0.015 (1.020), 763	−0.390	0.697
QIDS remission	0.036 (0.987), 901	−0.071 (0.991), 563	2.019	**0.044**
Responders HAMD	0.014 (0.953), 631	−0.107 (0.952), 596	−2.230	**0.026**
HAMD remission	0.027 (0.970), 681	−0.135 (0.927), 546	2.982	**0.003**

Note: Univariable analysis Nominal significant findings are reported in bold.

association did not achieve statistical significance in the GSRD sample, the consistent directional trend across both cohorts underlines its potential relevance. This is in line with recent genome-wide analyses showing substantial polygenic overlap between psychiatric disorders and sleep traits, particularly insomnia, with shared loci across schizophrenia, depression, and sleep phenotypes (O'Connell et al. 2021). Moreover, the concept of overlapping genetic risk between insomnia and depressive symptoms has been supported by polygenic risk score studies in MDD populations (Schubert et al. 2021). These results emphasize the role of sleep disturbances, both insomnia and hypersomnia, as transdiagnostic components of psychopathology, potentially driven by shared neurobiological pathways. Given their association with worse clinical outcomes, including chronicity and treatment resistance (Mak et al. 2025), future studies should integrate objective sleep measures and neurobiological correlates to explore whether SCZ-PGS contributes to a "sleep-impaired" depressive subtype.

Despite these promising results, our findings should be interpreted in the context of several limitations. First, although our GSRD cohort is relatively large and well characterized, the cross-sectional design does not allow causal inferences about the directionality or developmental trajectory of these associations. Second, we used a naturalistic definition of antidepressant nonresponse and TRD; while ecologically valid, this could introduce heterogeneity in treatment regimens, duration, and adherence. Third, although we used the most up-to-date SCZ GWAS summary statistics, the explanatory power of PGS for complex clinical phenotypes remains modest. The lack of replication in STAR*D of specific features suggests caution; however, the differences between the samples, such as a much milder baseline severity in the STAR*D, may explain the observed results. However, even when matching the samples for baseline severity, there were no more overlapping results, probably also due to the sample size reduction. In any case, also in the STAR*D, treatment outcome was correlated with SCZ-PGS and overall

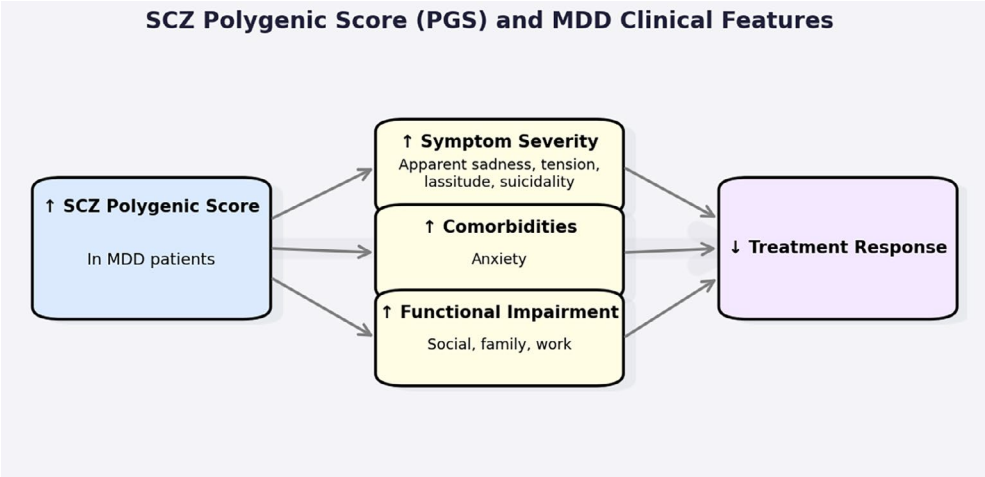

FIGURE 2 | Visual summary of the results. The model proposed is hypothetical and will need additional mediation analyses in adequately powered samples for support.

severity, though it could not replicate the antipsychotic finding due to the use of citalopram only in the treatment. Finally, *p*-values were not corrected for multiple testing given the confirmative framework, potentially inflating the type I error rate.

In summary, our study corroborates and extends prior evidence that SCZ genetic liability modulates the clinical features of depression. SCZ-PGS is associated with greater depressive severity, anxiety comorbidity, and possibly a higher likelihood of receiving antipsychotic augmentation. While the direct influence of SCZ-PGS on short-term antidepressant response appears small, it still holds potential as a contributory biomarker in understanding MDD heterogeneity. Future longitudinal studies, alongside advancements in PGS methodologies, larger GWAS datasets, and mechanistic research, will be essential to determine whether SCZ PGS can inform more precise treatment stratification and ultimately improve clinical decision-making in MDD.

Author Contributions

A.S., D.S., C.F., and J.M. conceptualized the research. S.K., J.Z., S.M., P.F., D.R., R.Z., B.T.B., and F.B. collected data, helped design the analysis, and interpret the results. Data visualization and writing of the original draft were completed by A.S., C.F., and G.F. All authors contributed to the review and editing of the manuscript.

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Conflicts of Interest

Dr. Rujescu served as a consultant for Janssen, received honoraria from Boehringer-Ingelheim, Gerot Lannacher, Janssen, and Pharmagenetix, received research/travel support from Angelini, Boehringer-Ingelheim, Janssen, and Schwabe, and served on advisory boards of AC Immune, Boehringer-Ingelheim, Roche, and Rovi. Dr. Souery has received grant/research support from GlaxoSmithKline and Lundbeck; and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Dr. Mendlewicz is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. Dr. Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultant or on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GlaxoSmithKline, Jazz, and Solvay. Dr. Montgomery has served as a consultant or on advisory boards for AstraZeneca, Bionevia, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Grunenthal, Intellect Pharma, Johnson and Johnson, Lilly, Lundbeck, Merck, Merz, M's Science, Neurim, Otsuka, Pierre Fabre, Pfizer, Pharmaneuroboost, Richter, Roche, Sanofi, Sepracor, Servier, Shire, Synosis, Takeda, Theracos, Targacept, Transcept, UBC, Xytis, and Wyeth. Dr. Serretti has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier and Taliaz. Dr. Kasper has received grant/research support from Lundbeck; he has served as a consultant or on advisory boards for Angelini, Biogen, Esai, Janssen, IQVIA, Lundbeck, Mylan, Recordati, Sage, and Schwabe; and he has served on speakers' bureaus for Aspen Farmaceutica S.A., Angelini, Biogen, Janssen, Lundbeck, Neuraxpharma, Recordati, Sage, Sanofi, Schwabe, Servier, and Sun Pharma. Dr. Baune received honoraria for serving as a consultant or on advisory boards unrelated to the present work for Angelini, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Meyers Squibb, Janssen, LivaNova, Lundbeck, Medscape, Neurotorium, Novartis, Otsuka, Pfizer, Recordati, Roche, Rovi, Sanofi, Servier, and Teva. The other authors declare no potential conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** SCZ-PGS correlations in the GSRD less severe subset. **Table S2:** SCZ-PGS associations in the GSRD less severe subset.