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THOUGHT LEADERS INVITED REVIEW

Mood disorders polygenic scores influence clinical outcomes of major psychiatric disorders

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Polygenic scores (PGS), summarizing the cumulative contribution of common genetic variants to psychiatric phenotypes, are increasingly investigated as putative predictors of treatment response and illness course. In major depressive disorder (MDD), several studies have associated higher MDD PGS with a modestly increased risk of nonresponse, lower remission rates, and treatment resistance. Conversely, bipolar disorder (BD) PGS have yielded more heterogeneous findings, with largely null or weak associations in unipolar depression but a possible on lithium response in BD cohorts, while lower MDD PGS showed a more consistent beneficial effect on lithium response in BD. MDD PGS may also have a modulating effect on clinical features of schizophrenia and a range of other psychiatric disorders. Nonetheless, the variance explained remains limited and predictive power improves only marginally when PGS are used in isolation. Integrative approaches that combine clinical predictors, environmental measures, and biomarker data appear to enhance prediction over genetics alone, which is increasing due to the most recent large genomewide studies. However, ancestral diversity remains limited, with most research conducted in Caucasian samples. Taken together, current evidence supports the incremental value of MDD and BD PGS in informing prognosis and treatment response, though clinical implementation remains premature. Replication in ancestrally diverse samples, integration with dimensional phenotypes, and improved modeling strategies will be essential to translate genetic liability into clinically actionable insights in precision psychiatry.

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Introduction

Major depressive disorder (MDD) and bipolar disorder (BD) are two of the most prevalent and disabling psychiatric conditions worldwide, contributing significantly to the global disease burden through chronic distress, functional impairment, and elevated mortality risk (1, 2). Despite advances in clinical assessment and psychopharmacology, predicting disease onset, course, and treatment response remains a central challenge for mental health practitioners. Traditional clinical features alone often fail to capture the broad heterogeneity of mood disorders, highlighting the need for more precise, biologically informed markers (3). In the past decade, genome-wide association studies (GWAS) have substantially expanded our understanding of the genetic architecture of psychiatric disorders, culminating in the development of polygenic scores (PGS) as potential tools for disentangling genetic contributions to complex psychiatric phenotypes (4).

PGS aggregate the effects of hundreds to thousands of common genetic variants, each exerting a small effect, into a single quantitative index of genetic liability. This approach is particularly relevant for mood disorders: MDD and BD, like most psychiatric conditions, are highly polygenic, with hundreds of variants collectively accounting for a proportion of disease risk (5, 6). The same polygenic influences may also shape symptom severity, comorbidities, and response to pharmacological or psychosocial interventions in other psychiatric disorders. Over the last few years, an increasing number of studies have leveraged PGS to investigate whether individuals carrying a higher genetic burden for MDD or BD exhibit specific clinical features (e.g., remission, treatment resistance, or different patterns of psychiatric comorbidity). Consequently, an evidence base is emerging that seeks to integrate these genetic features with traditional clinical factors, hoping to refine prognostic models and personalize treatment choices.

Given the rapidly evolving landscape of genetic research, there is a need to synthesize findings on how MDD and BD PGS relate to psychiatric outcomes.

Recent reviews provide a useful overview about the potential impact of PGS on treatment outcome (7, 8); however, the broad approach in these previous reviews does not focus on mood PGS alone and it does not include a substantial number of very recent studies across all major psychoses.

In this review, we present a narrative synthesis of the literature investigating MDD and BD PGS in relation to treatment outcomes (response, remission, and treatment resistance) and other clinically relevant phenotypes (comorbidity, illness course, and environmental exposures) in major psychoses.

Results

Treatment Outcome

Major Depression The first application of PGS in treatment outcome was reported in 2013 (9). The study reported a meta-analysis of three genome-wide pharmacogenetic studies—GENDEP ($N = 672$), MARS ($N = 604$), and STARD ($N = 980$)—in individuals with MDD treated with various antidepressants for up to 12 weeks, and derived PGS from the GENDEP and MARS cohorts which, when applied to the STARD sample, modestly predicted antidepressant response by explaining between 0.5% and 1.2% of the variance in percentage improvement and remission rates, the very small sample size of the original samples from which PGS have been calculated may explain the low predictive power in this early study. A subsequent study (10) examined two large cohorts, NEWMEDS ($N = 1791$) and again STARD ($N = 1107$), specifically testing whether BD PGS, derived from the largest Psychiatric Genomics Consortium (PGC) BD GWAS of that time (7481 cases and 9250 controls), could predict antidepressant response in MDD; however, the analyses revealed no significant association, with BD PGS explaining less than 0.01% of variance overall for selective serotonin reuptake inhibitors (p values ranging from 0.829 to 0.934) and only slightly higher yet nonsignificant variance (0.15%–0.34%, p ranging from 0.184 to 0.999) in the norepinephrine reuptake inhibitor subgroup. Also in this case, the GWAS sample where PGS have been calculated was

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relatively small and much smaller than the following ones that have been used later, which led to PGS with much less predictive power (11).

A few years later, García-González *et al*. (12) investigated MDD PGS in antidepressant treatment response across seven pharmacogenetic studies, with primary analyses in GENDEP ($n = 736$) and STARD ($n = 1409$) and validation in five additional independent samples totaling 3756 subjects, but found that MDD PGS did not significantly predicted symptom improvement or remission, as p values remained greater than 0.1 across nine significance thresholds, though rarer variants, $p < 0.0001$, showed a modest trend. Other than the relatively small original GWAS sample size (13), in this and many older studies PGS were calculated without more recently optimized Bayesian tools (14) and multiple thresholds were used, moreover the target samples heterogeneity may have influenced results. Indeed, MDD is recognized to be a more heterogeneous disorder when compared to other major psychoses, as evidenced by the lower genetic heritability, and this constitutes a challenge in biological studies. In fact, in a more homogeneous study some more significant results were reported. Ward *et al*. (15) analyzed 760 patients with MDD from three cohorts (GENDEP, AMPS–1, and AMPS–2) treated with escitalopram, nortriptyline, or citalopram/escitalopram over 8–12 weeks, computing MDD PGS and for neuroticism (NEU PGS) using GWAS data from the largest studies at the time (16, 17); in this study meta-analyses revealed for the first time some nominal associations, such as MDD PGS at $p < 5 \times 10^{-5}$ showing a β of -0.019 ($p = 0.009$) for 4–week response and NEU PGS at $p < 0.1$ showing a β of -0.017 ($p = 0.03$) for 8–week response; however, the variance explained remained very low ($\leq$1.2%), and the associations did not survive stringent correction for multiple testing.

The first community sample, including a larger and more powered sample, was studied in 2020, it examined antidepressant treatment resistance using prescription data from the Generation Scotland: Scottish Family Health Study (GS:SFHS) and the GENDEP cohort, with a meta-analysis of 4213 individuals (358 cases and 3855 controls) and a separate GWAS on stages of resistance (n = 3452) (18). PGS using summary statistics for MDD and BD revealed again nominal associations between treatment resistance and MDD PGS at thresholds of <0.1, <0.5, and <1, whereas BD PGS showed no significant relationship. This study performed in a relatively large sample therefore confirmed previous MDD PGS results.

Treatment-resistant depression (TRD) was then analyzed in the context of esketamine response by analyzing 527 European-ancestry individuals from two phase III trials (SUSTAIN–2 and TRANSFORM–3, the latter restricted to those with age of onset $<$55 years), where the primary outcome was the percentage change in Montgomery–Åsberg Depression Rating Scale (MADRS) score at 4 weeks (19); the GWAS identified a significant Single Nucleotide Polymorphism (SNP) in IRAK3 (rs11465988, $p = 3.57 \times 10^{-8}$, $\beta = -51.6$, SE = 9.2) and a gene-level association for NME7 ($p = 1.73 \times 10^{-6}$), and PGS based on depressive symptoms (20) were nominally associated with esketamine response ($p = 0.001$, $\beta = -3.1$, SE = 0.9), whereas BD PGS (21) was not significantly associated ($p = 0.076$ for MADRS change, $p = 0.141$ for remission), expanding the potential role for depressive symptom genetic loading in antidepressant outcome also to esketamine efficacy, but not for bipolar liability. This finding is of interest given that it was the first focusing on the narrow phenotype of TRD and it could reduce the heterogeneity of antidepressant response by focusing on esketamine treatment outcome (22–25).

Shortly after, the focus shifted to late-life antidepressant response in 335 older adults ($\geq$60 years) with MDD treated with venlafaxine XR over 12 weeks in the IRL–GREY (26) clinical trial (27); although the GWAS did not reveal genome-wide significant SNPs for remission or symptom improvement, and PGS constructed for depression and Alzheimer's disease were not significantly associated with treatment response, a PGS for cardioembolic stroke was significantly linked to nonremission [OR = 0.63, 95% confidence interval (CI) = 0.48–0.83, $p = 0.001$, permutation p = 0.006], suggesting that vascular factors, frequently associated with depression, might play a role in antidepressant resistance among older individuals, as suggested by recent genetic correlation studies between MDD and cardiometabolic factors (28). However a later reanalysis of the same sample investigated antidepressant response in late–life depression in 342 adults aged $\geq$ 60 from the same IRL–GREY study with the same treatment, and observed that while the BD PGS was nominally associated with better remission (OR = 0.75, 95% CI = 0.58–0.97, $p = 0.031$) and symptom improvement ($\beta = 4.27$, SE = 2.17, $p = 0.049$), the MDD was not associated with treatment outcomes, though with a trend in the same direction of the other papers here reviewed ($p = 0.086$) and intriguingly, the ADHD PGS was nominally associated with higher odds of remission (OR = 1.36, 95% CI = 1.07–1.73, $p = 0.011$), contrary to a previous finding (29). Though none of these associations survived Bonferroni correction, suggesting that in late-life depression genetic predictors of treatment response may partially differ from those in younger populations (30), trends were mostly in line with other studies. The BD and MDD PGS results difference across the two studies on the same sample could be explained by the use in the second sample of PGS calculated excluding 23andme data, that may be less powerful in explaining phenotypic variance given the self-report bias (31).

In 2021, the European Group for the Study of Resistant Depression (GSRD) sample of 1148 patients with MDD was used to assess the relationship between PGS for BD, MDD, and neuroticism (NEU) with treatment nonresponse and treatment resistance (TRD defined as failure of two or more antidepressants) (32); we found that that MDD PGS was nominally associated with non–response ($p = 0.032$) in the same direction of previous studies, while BD PGS and NEU PGS did not show significant effects. In a following meta-analysis, we examined PGS for MDD, BD, and NEU in relation to antidepressant nonresponse and nonremission in a larger sample of 3637 and 3184 patients respectively from six European clinical samples, and confirmed that the MDD PGS was nominally associated with nonresponse (OR = 1.10, 95% CI = 1.02–1.19, $p = 0.013$, pseudo–$R^2 = 0.24$%) and nonremission (OR = 1.14, 95% CI = 1.04–1.24, $p = 0.004$, pseudo–$R^2 = 0.57$%) at specific p–value thresholds, while BD PGS showed no significant association; however, though none of these associations survived correction for multiple testing, the observed trends of MDD PGS effects remained in a relatively large and heterogeneous target sample (33).

A smaller, but with a more complex design study, investigated predictors of clinical outcome in 174 patients with TRD admitted to a specialist inpatient unit where patients received a multimodal treatment regimen including pharmacotherapy, cognitive behavioral therapy (CBT), behavioral activation, and, if indicated, electroconvulsive therapy (34); while clinical predictors such as later age of onset, a higher number of previous depressive episodes, and lower treatment resistance (as measured by the Maudsley Staging Method) were significantly associated with a favorable response, PGS for MDD, BD, and schizophrenia (SCZ) did not predict treatment outcome, as none of the genetic variables reached significance in either univariate or multivariate analyses, suggesting that in the context of intensive inpatient treatment for TRD, clinical factors may overshadow the modest effects of genetic liability, the relatively small target sample may also have influenced results. Indeed, variance explained in the range of 1%–2% need larger samples to be detected.

In a large population study, we analyzed TRD using primary care records from UK Biobank ($n = 230{,}096$, with MDD cases numbering 19,979 and TRD cases 2430) and the EXCEED cohort ($n = 8926$, with 1271 MDD cases and 159 TRD cases) (29), finding that while MDD PGS robustly predicted MDD diagnosis ($p = 1.89 \times 10^{-71}$ in UKB and $p = 6.05 \times 10^{-6}$ in EXCEED), PGS for BD were only weakly associated with MDD in UKB and not in EXCEED, and crucially, when comparing TRD with non–TRD MDD, these PGS did not show significant differences after correction for multiple testing, although MDD PGS showed a nominal positive correlation ($p = 0.028$). This study underlines the importance of investigating large target samples that may overcome the outcome heterogeneity observed in MDD, though populations samples such as this one may add other stratification factors when compared to clinical samples.

Placebo response was examined for the first time, versus antidepressant treatment, in 1364 patients with MDD from seven randomized, double–blind, placebo–controlled vortioxetine trials, with an additional self–reported validation sample from 23andMe ($N = 642$), constructing PGS for antidepressant response as well as for MDD and BD, NEU, subjective well–being, and cognition (35); although no PGS reached significance

after Bonferroni correction, analyses showed that higher MDD PGS was nominally linked to a better placebo response on measures of somatic anxiety ($\beta = 0.54$, $p = 0.011$), suggesting that genetic predisposition may influence not only drug response but also placebo effects, albeit with small effect sizes and limited clinical utility on their own. It remains to be investigated whether MDD PGS effects are limited to antidepressant treatment or have a disease course modulatory effect.

PGS for antidepressant response (PGS–AR), computed from GWAS summary statistics (36), was then investigated with electroencephalogram (EEG) biomarker data in a sample of 1123 participants (including 1061 psychiatric patients and 62 healthy controls) to determine whether a specific EEG component (component 4) could predict treatment response in MDD (37); in men, PGS–AR was significantly associated with EEG component 4 ($\beta = 0.172$, $R^2 = 2.91\%$, $p = 0.000567$), and this EEG component significantly predicted symptom improvement in an independent iSPOT–D sample ($\beta = -0.153$, $R^2 = 2.3\%$, $p = 0.019$) as well as in a dataset of rTMS plus psychotherapy patients ($\beta = -0.230$, $R^2 = 5.3\%$, $p = 0.022$), although these associations were not observed in women. This study investigated PGS-AR, which in theory may be more powerful than MDD PGS, but it should be considered that the origin samples to calculate PGS-AR are usually much smaller that MDD GWAS samples, therefore the power is much reduced. However, the value of this study is to be a proof–of–concept that combining genetic and neurophysiological markers may enhance the prediction of antidepressant outcomes.

PGS for antidepressant and lithium response were then investigated in a large sample of 4572 patients with MDD from three Swedish cohorts (PREFECT, iCBT, and STAGE) using three distinct definitions of TRD (38), and found that while the PGS-AR did not significantly differ between TRD and non–TRD groups (e.g., broad definition: mean difference $= -0.015$, $p = 0.631$), the PGS for lithium response was significantly higher in TRD cases (e.g., broad definition: mean difference $= 0.094$, $p = 0.003$; logistic regression showed an OR of 1.12 per SD increase, 95% CI $= 1.04$–1.20, $p = 0.003$), with a dose–response effect evident in the top PGS quartile ($P_{trend} < 0.005$), suggesting that TRD may be characterized by a higher genetic predisposition to respond to lithium and emphasizing the pleiotropic effects of PGS in both MDD and BD and, from a clinical point, supporting the potential utility of a targeted lithium use in TRD.

We recently examined the interaction between PGS for mood disorders, including MDD and BD, and environmental factors in the UK Biobank (with sample sizes ranging from 33,000 to 380,000) (39), finding that while both PGS and environmental variables had additive effects on well-being, significant interactions emerged such that higher MDD PGS intensified the negative impact of recent stress on loneliness ($\beta = 0.0156$, SE $= 0.0025$, $p = 3.20 \times 10^{-10}$) and BD PGS interacted with stress to predict lower household income ($p = 1.17 \times 10^{-4}$), even though these interactions explained only an additional 0.01%–0.02% of variance, supporting the differential susceptibility hypothesis and suggesting that genetic liability for mood disorders can modulate the effects of environmental adversity, as it will be discussed in the conclusion section.

A secondary analysis of the Early Medication Change (EMC) trial was recently performed involving 481 patients with MDD (compared with 3215 controls from the Heinz Nixdorf Recall study) undergoing an 8–week treatment algorithm starting with escitalopram and switching to venlafaxine or lithium (40), and although the MDD PGS was significantly associated with disorder status (Nagelkerke's $R^2 = 2.48\%$, $p < 1 \times 10^{-12}$), it did not predict treatment outcomes such as early improvement, response, or remission (with Nagelkerke's R^2 values ranging from 0.007% to 0.256%); however, the relatively small sample size of the target sample may be considered as a limitation also of this study.

Following with the large series of very recent studies, Monistrol–Mula *et al*. (41) explored the impact of polygenic liability to various mental disorders on COVID–19 outcomes in 4405 individuals with a history of depression from the Australian Genetics of Depression Study (AGDS), and found that the MDD PGS was significantly associated with higher COVID–19 burnout ($\beta = 0.36$, SE $= 0.12$, $p = 0.003$, adjusted $R^2 = 0.089$), with individuals in the top 10% having 4.17–fold higher odds of burnout (95% CI $= 1.47$–11.86), while the BD PGS showed a trend toward a protective effect against burnout that did not survive multiple testing, suggesting that genetic liability for depression may predispose individuals to greater psychological distress during the pandemic through its influence on anxiety, which fully mediated the observed association.

Pregnancy and postpartum are relevant periods for depression (42) and they were the focus of another study that investigated whether PGS for MDD and BD predicted antidepressant treatment trajectories in a Danish cohort of 2316 women with mood disorders (43), but found no significant associations between these PGS and treatment trajectories (categorized as continuers, early discontinuers, late discontinuers, or interrupters), with clinical factors such as higher prepregnancy antidepressant dose, longer treatment duration, and prescription of multiple antidepressant classes being the primary predictors of continued antidepressant use, thus suggesting that, at least in the perinatal period, treatment trajectories are largely driven by clinical severity and possibly by other environmental factors rather than genetic liability.

Positive results have also been reported in another recent study aimed at validating an antidepressant response algorithm across multiple electronic health record (EHR) systems from Vanderbilt University Medical Center, the All of Us Research Program and the Mass General Brigham Healthcare System (44). It demonstrated that higher polygenic risk scores for MDD (OR $= 1.07$, $p = 2.84 \times 10^{-8}$), and BD (OR $= 1.04$, $p = 1.99 \times 10^{-3}$) were significantly associated with poorer antidepressant response, with an estimated heritability of antidepressant response of 3.84% (SE $=$ 0.007) and significant genetic correlations with these psychiatric traits (rg $= 0.23$ for MDD, rg $= 0.15$ for BD), thereby supporting previous findings on MDD PGS though the overall predictive power of PGS remains modest.

Genetic analyses are mainly performed in Caucasian populations, but information on Asians is also needed, given the known differences in the genetic background (45, 46). Shao *et al*. (47) examined the association between MDD PGS and early antidepressant efficacy in 912 Han Chinese patients with nonpsychotic MDD (aged 18–65, with baseline HAM–D17 $\geq$ 18 and medication–free for at least 2 weeks), and reported that a higher MDD PGS was significantly associated with a lower percentage reduction in HAM–D17 scores after 2 weeks ($p = 0.009$; Spearman $r = -0.075$, $p =$ 0.024; in multivariate regression, $\beta = -4.086$, $p = 0.039$, adjusted $R^2 =$ 0.086), no significant interaction with negative life events was observed, suggesting that the direction of the effect may be the same when compared to Caucasians and that the effect is quite high, this is quite encouraging for generalizability of the MDD PGS effect.

A larger longitudinal population study utilized data from the iPSYCH 2015 sample in Denmark to investigate polygenic liabilities in early–onset MDD (diagnosed between ages 10 and 25, $N = 10{,}577$) and identified four treatment trajectories over 7 years using latent class growth analysis, brief contact, prolonged initial contact, later re–entry, and persistent contact, and found that the MDD PGS was nominally associated with the later re–entry trajectory (OR $= 1.09$, 95% CI $= 1.02$–1.17, $p = 0.01$) and significantly associated with continued antidepressant treatment in primary care (OR $= 1.11$, 95% CI $= 1.05$–1.17, $p = 0.0003$), while BD PGS did not show significant associations, suggesting that the MDD PGS effect may be detected also in early–onset depression and during longitudinal clinical course. This study also supports the usefulness of large population sample, that, despite the limitations inherent to registries, may well contribute to the definition of the genetic modulating effects (48).

Bipolar Disorder MDD PGS were also studied on lithium response in patients with BD using data from the Consortium on Lithium Genetics (ConLi + Gen), comprising 2586 patients (with analyses stratified by ethnicity: multiethnic, European, and Asian subsamples) (49); employing weighted PGSs constructed from a large PGC GWAS (135,458 MDD cases and 344,901 controls), the authors found that higher MDD PGS were significantly associated with poorer lithium response, with continuous outcomes showing significant R^2 values of approximately 0.8% in the multiethnic sample (and similar findings in the European subsample). Stratified analyses showed that patients in the lowest quartile of MDD PGS had significantly better outcomes (e.g., OR $= 1.54$ in the multiethnic sample and OR $= 1.75$ in Europeans). This study suggested for the first time that patients with BD with lower polygenic liability for depression may

represent a distinct lithium-responsive biotype; sensitivity analyses using unrelated trait PGS (bone mineral density) confirmed the specificity of the effect.

Lithium response was again the focus in patients with BD in the same largest sample collected so far described before ($N = 2283$ from ConLi + Gen) and the study examined MDD PGS associated with treatment outcomes as measured by the Alda scale (50); the study found higher MDD PGS (OR = 1.61, $p = 0.04$) significantly associated with poorer lithium response, and that a meta–analytic approach combining SCZ and MDD PGS into a MET2–PGS improved prediction (OR = 2.54, $p = 0.002$, with Nagelkerke's R^2 of 0.91%), whereas BD PGS alone did not significantly predict response; functional pathway analyses of MET2–PGS implicated histone modification and glucose metabolism pathways, suggesting epigenetic and metabolic mechanisms may underlie lithium efficacy. This result is in line with the previously reported detrimental effect of SCZ PGS (51) and suggests a synergic effect of both SCZ and MDD PGS on BD maintenance outcome.

The same ConLi + Gen sample was again analyzed with a machine–learning approach in a subsample of 1034 patients with BD to predict lithium response using both clinical predictors and PGS for SCZ and MDD (52); the study demonstrated that while PGS alone explained only modest variance (1.2% in linear models and 2.0% in nonlinear models), combining PGS with clinical variables improved prediction to 4.7% (and up to 13.7% in PGS–stratified models), with patients in the lowest quartile of MDD PGS being 67.7% more likely to respond to lithium than those in the highest quartile (OR = 1.68, 95% CI = 1.14–2.47, $p = 0.009$). This study clearly underlines the benefit of a combined model with the perspective of a potential clinical utility of integrating clinical and genetic risk information for personalized treatment stratification.

Lithium pharmacogenetics in BD was also investigated by developing a lithium response polygenic score (Li + PGS) in the mentioned large ConLi + Gen cohort ($N = 2367$) and replicating the findings in PsyCourse ($N = 89$) and BipoLife ($N = 102$) cohorts (53); lithium response, measured via the ALDA scale (both continuously and categorically with a cutoff of 7), was significantly predicted by Li + PGS (categorical outcome: $p = 9.8 \times 10^{-12}$, $R^2 = 1.9\%$; continuous outcome: $p = 6.4 \times 10^{-9}$, $R^2 = 2.6\%$), with patients in the highest Li + PGS decile having 3.47–fold higher odds of a favorable response (95% CI = 2.22–5.47), and gene–based pathway analysis implicated cholinergic and glutamatergic systems, thereby reinforcing the notion that lithium responders may have a distinct genetic profile in addition to the previously reported lower polygenic liability for depression.

Collectively, these studies (Table 1), spanning from 2013 to 2025 and incorporating diverse samples, from large-scale meta-analyses and clinical trials to population-based and EHR studies, strongly suggest that MDD PGS show modest but consistent associations with both disorder severity susceptibility and treatment outcomes (with higher MDD polygenic load generally predicting poorer antidepressant or lithium response). BD PGS have shown a less robust predictive value for antidepressant response in MDD, but they may play a role in influencing lithium response in BD when considered in conjunction with other PGS. In any case the overall variance explained by these genetic predictors remains low, underscoring the complexity of treatment response phenotypes and the need for integrating genetic information with clinical, environmental, and other biological markers to enhance predictive accuracy.

Outcome-Related Traits A series of papers investigated clinical aspects that, though not directly measuring short-term treatment outcome, may inform about the possible influence of PGS. Kowalec *et al*. (54) analyzed 24,706 individuals with SCZ from the Swedish national registers, with a genomic subset of 4936 cases, to investigate clinical, demographic, and genetic factors associated with treatment-resistant schizophrenia (TRS), defined both by clozapine prescription ($N = 4813$) and by clozapine prescription or antipsychotic polypharmacy for $\geq$ 90 days ($N = 13,779$); although they found that a higher SCZ family history burden [highest quartile vs. lowest quartile: OR = 1.31, 95% CI = (1.19–1.42), $p = 4.8 \times 10^{-8}$] and lower premorbid IQ in males (per 1 SD decrease: OR = 0.94, 95% CI = [0.90–0.98], $p = 0.002$) were robust predictors of TRS, none of the PGS, MDD or BD reached significance ($p > 0.1$ for both), though both PGS showed a nonsignificant trend in the direction of increasing TRS.

A smaller but well-designed study conducted an integrative genomic–epigenomic analysis in 44 patients with refractory psychosis treated with clozapine [31 with SCZ (70.45%), 9 with schizoaffective disorder (20.45%), and 4 with BD (9.09%)], computing PGS for BD and MDD, and found that BD PGS was significantly associated with clozapine metabolic ratio (pseudo-$R^2 = 0.2080$, $p = 0.0008$, adjusted $p = 0.0189$), while MDD PGS was only nominally associated with clozapine dose (pseudo-$R^2 = 0.386$, $p = 0.0035$, adjusted $p = 0.0759$), suggesting that bipolar genetic liability could influence clozapine metabolism, and, probably more interesting, that MDD genetic risk may lead treating clinicians to raise the dose possibly for an observed poor response (55).

A more recent study focused more directly on the interplay of MD and BD PGS with clinical and environmental factors (56). The study examined data from the AGDS ($N = 14,146$; 75% female, mean age = 44.0 years) to assess associations between PGSs for multiple mental disorders, MDD and BD, and exposure to 32 stressful life events (SLEs) categorized by childhood, past-year, lifetime, and cumulative events. Using logistic and linear regression models adjusted for age and sex with false discovery rate (FDR) correction, they found that higher MDD PGS was significantly associated with increased odds of exposure to all childhood SLEs (ORs = 1.07–1.12, p's < 0.013, FDR-corrected), as well as with specific adverse events such as physical assault [OR = 1.06, 95% CI = (1.02–1.11), $p = 0.006$], unwanted or uncomfortable sexual experiences, sexual assault [OR = 1.10, 95% CI = (1.05–1.16), $p < 0.001$], severe human suffering [OR = 1.17, 95% CI = (1.05–1.30), $p = 0.003$], life-threatening illness or injury [OR = 1.09, 95% CI = (1.03–1.15), $p = 0.003$], and assault with a weapon [OR = 1.12, 95% CI = (1.04–1.21), $p = 0.003$]; additionally, higher MDD PGS was associated with increased cumulative SLEs (ORs = 1.05–1.24, FDR-corrected p's < 0.05), whereas higher BD PGS was associated with lower odds of experiencing physical assault [OR = 0.95, 95% CI = (0.91–0.99), $p = 0.014$], major financial troubles [OR = 0.93, 95% CI = (0.88–0.98), $p = 0.004$], and living in unpleasant surroundings [OR = 0.92, 95% CI = (0.87–0.98), $p = 0.008$], as well as with fewer reported childhood SLEs [OR = 0.97, 95% CI = (0.95–0.99), $p = 0.01$]. Results from this complex study may suggest that, while genetic liability for depression may predispose individuals to greater exposure to stress, BD genetic risk appears inversely related to such exposure. The large sample and the evaluation of stressful life events are positive aspects of the study that add to the overall outcome domain and are in line with previous evidence therefore starting to identify specific modulating effects of MDD versus BD PGS.

A converging evidence comes from another study (57), that used data from two population-based cohorts, the Avon Longitudinal Study of Parents and Children (ALSPAC; $N = 5521$, mean age = 11.8 years, SD = 0.14, 50.3% female) and the Twins Early Development Study (TEDS; $N = 4625$, mean age = 11.27 years, SD = 0.69, 53.2% female), to compute MDD PGS among other traits and to examine their associations with psychopathology symptoms measured by the Short Mood and Feelings Questionnaire (SMFQ) and the Strength and Difficulties Questionnaire (SDQ); the study found that the depression PGS was significantly associated with the symptom "not enjoying anything" ($r = 0.04$) and with "being bullied" ($r = 0.06$) on the peer problems subscale, supporting the evidence that genetic risk for depression may be broadly influencing the complex interplay with environmental stressors and possibly reducing the heterogeneity of treatment outcome (58).

Another interesting possible effect, diagnostic transition, was recently investigated (59). The study included 10,565 individuals from a Danish registry with eating disorders (Anorexia nervosa [AN], $n = 6901$; Bulimia nervosa [BN], $n = 1417$; Eating Disorder Not Otherwise Specified [EDNOS], $n = 2247$) and calculated PGS for 422 traits including MDD and BD using LDpred2 and meta-PGS approaches; the study found that a higher PGS for MDD was significantly associated with a 15% greater hazard of transitioning from anorexia nervosa to either bulimia nervosa or EDNOS (HR = 1.15 per SD increase, $p < 1.57 \times 10^{-4}$), whereas the BD PGS was not significantly associated with diagnostic transitions. Though not directly investigating outcome, results from this study are interesting because

Table 1. Summary of studies investigating MDD and BD PGS and outcome

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Amare *et al.*, 2021	MDD PGS and lithium response in BD	Analysis within ConLi + Gen; multiethnic sample with subgroup analyses	Lithium treatment; response measured by the Alda scale (continuous and categorical)	BD patients: Multiethnic $N = 2586$ (European: $N = 2366$; Asian: $N = 220$)	Higher MDD PGS associated with poorer lithium response (multiethnic: continuous $R^2 = 0.8\%$, categorical $R^2 = 0.7\%$; European quartile OR = 1.75, decile OR = 1.74; Asian: nominal, $p = 0.034$)	Lower polygenic load for MDD in patients with BD predicts better lithium response
Amare *et al.*, 2023	Lithium response PGS in BD	Cohort study in ConLi + Gen with replication in PsyCourse ($N = 89$) and BipoLife ($N = 102$)	Lithium treatment; response measured by the ALDA scale (categorical and continuous outcomes)	ConLi + Gen: $N = 2367$; Replication cohorts: PsyCourse $N = 89$, BipoLife $N = 102$	Li + PGS associated with lithium response in ConLi + Gen (categorical: $p = 9.8 \times 10^{-12}$, $R^2 = 1.9\%$; continuous: $p = 6.4 \times 10^{-9}$, $R^2 = 2.6\%$); patients in the 10th decile had 3.47-fold higher odds (95% CI: 2.22–5.47); replication $p = 3.9 \times 10^{-4}$, $R^2 = 0.9\%$	Lithium response in BD is partly genetically determined, with evidence implicating cholinergic and glutamatergic pathways
Cearns *et al.*, 2022	PGS-guided stratification for lithium response in BD	Retrospective analysis with machine-learning; training set $n = 692$, test set $n = 342$	Lithium treatment; response via Alda scale	Patients with BD from ConLi + Gen: $N = 1034$	Combining PGS (PGS-SCZ and PGS-MDD) with clinical predictors improved variance explained to 5.1% (linear models) and up to 13.7% in stratified models; lower MDD PGS associated with better response (OR = 1.677, 95% CI = 1.14–2.47, $p = 0.009$)	Integrating PGS with clinical data enhances lithium response prediction in BD
Elsheikh *et al.*, 2024	BD and MDD PGS effects on late-life antidepressant response	12-week trial analysis (IRL-GRey study) in adults aged ≥60 years	Venlafaxine XR titrated from 37.5 mg/day up to 300 mg/day for 12 weeks	Late-life depression: $N = 342$ adults	BD PGS was nominally associated with remission (OR = 0.75, 95% CI = 0.58–0.97, $p = 0.031$) and with symptom improvement (β=4.27, SE = 2.17, $p = 0.049$); MDD were not significant; ADHD PGS nominally (OR = 1.36, $p = 0.011$)	In late-life depression, BD genetic liability may modestly influence treatment response
Fabbri *et al.*, 2021	MDD/BD PGS associations with treatment-resistant depression (TRD)	Retrospective cohort analysis using primary care records (UKB and EXCEED)	TRD defined as ≥2 antidepressant switches (each ≥6 weeks)	UKB: MDD $n = 19979$ (TRD $n = 2,430$); EXCEED: MDD $n = 1271$ (TRD $n = 159$); UKB total = 230,096, EXCEED = 8926	MDD PGS nominally associated with TRD vs. non-TRD (p = 0.028); BD PGS not significant (p = 0.07)	TRD in MDD may involve genetic liabilities beyond MDD and BD (e.g. ADHD
Fabbri *et al.*, 2024	MDD/BP PGS effects on wellbeing	Cross-sectional analysis; sample size varied from 33,000 to 380,000 (UK Biobank)	Observational study	UK Biobank participants (using mood disorder PGS among others)	Higher MDD and BP PGSs interacted with environmental stress (e.g., BP PGS increased odds of lower income, $p = 1.17 \times 10^{-4}$); PGS × E interactions added ~0.01%–0.02% variance	Genetic liability for mood disorders modulates the impact of adverse/protective environments on well-being
Fanelli *et al.*, 2021	MDD PGS in predicting antidepressant nonresponse in MDD	Cross-sectional analysis in the European Group for the Study of Resistant Depression (GSRD)	Antidepressant treatment; patients classified as responders, nonresponders (failure of 1), or TRD (failure of ≥2)	Patients with MDD from GSRD: $N = 1148$	MDD PGS was nominally associated ($p = 0.032$); BD PGS was not significant	Increased MDD genetic liability may indicate an MDD subtype less responsive to treatment
Fanelli *et al.*, 2022	Mood disorder PGS impact on antidepressant nonresponse/ nonremission	Meta-analysis across six European clinical samples; PGS computed at eight thresholds	Antidepressant treatment; outcomes: nonresponse and nonremission	Nonresponse sample: $n = 3637$; Nonremission sample: $n = 3184$	MDD PGS was nominally associated with nonresponse (OR = 1.10, 95% CI = 1.02–1.19, $p = 0.013$) and nonremission (OR = 1.14, 95% CI = 1.04–1.24, $p = 0.004$); BD PGS not significant	A higher genetic burden for depression may increase the risk of poor antidepressant outcomes
García-González *et al.*, 2017	MDD PGS prediction of antidepressant response	Analysis in GENDEP ($n = 736$) and STAR*D ($n = 1409$) with validation in five independent studies	Antidepressants administered over 12 weeks	Combined discovery sample: $N \approx 2145$; Validation: total $n = 3756$	MDD PGS not associated with antidepressant response ($p > 0.1$ across nine thresholds). rarer variants, $p < 0.0001$, showed a modest trend	MDD PGS modest effect in line with other reports

(*continued*)

Table 1—*Continued*

Study	Objective	Design	Treatment	Subjects	Findings	Implications
GENDEP Investigators *et al.*, 2013	Antidepressant response polygenic prediction	Meta-analysis of three GWAS pharmacogenetic studies; 12-week treatment duration	GENDEP: escitalopram (10–30 mg/day) or nortriptyline (50–150 mg/day); MARS: various antidepressants (naturalistic inpatient setting); STAR*D: citalopram (20–60 mg/day)	Total $N = 2256$ individuals with MDD; GENDEP: $N = 672$; MARS: $N = 604$; STAR*D: $N = 980$	PGS derived from GENDEP/MARS significantly predicted STAR*D improvement (PGS explained 0.5%–1.2% of variance, $p = 0.005$–0.048) and remission (PGS explained 0.8%–1.2% of variance, $p = 0.017$–0.041)	In this early study, the small origin sample size may limit informativeness
Li *et al.*, 2020	Depressive PGS influence on esketamine response in TRD	GWAS and PGS analysis in two phase III trials (SUSTAIN-2 and TRANSFORM-3); analysis in European ancestry (TRANSFORM-3 limited to onset <55 years)	Esketamine treatment; primary outcome: % change in MADRS at 4 weeks; also responder and remission status	Total sample: $N = 527$ (from SUSTAIN-2 [$n \approx 598$] and TRANSFORM-3 [$n = 95$], with inclusion criteria applied)	Depressive symptom PGS was nominally associated with MADRS change ($p = 0.001$, $\beta = -3.1$) and with remission ($p = 0.002$); BD PGS showed a trend of association ($p = 0.076$)	Genetic loading for depressive symptoms may modestly affect esketamine efficacy in TRD
Liu *et al.*, 2024	PGS impact on perinatal antidepressant treatment trajectories	Retrospective cohort study from Danish registers	Antidepressants prescribed prepregnancy; trajectories: continuers, early/late discontinuers, interrupters	Women with affective disorders: $N = 2316$; Trajectory distribution: continuers 38.2%, early discontinuers 22.7%, late discontinuers 23.8%, interrupters 15.3%	PGS for MDD and BD were not associated with treatment trajectories (e.g., for continuers vs. early discontinuers: MDD PGS RRR = 0.93, 95% CI = 0.81–1.06)	Antidepressant use during the perinatal period appears driven by clinical factors rather than by genetic liability for mood disorders
Marshe *et al.*, 2021	Depression PGS impact on late-life antidepressant response	GWAS and PGS analysis in a 12-week trial in older adults (≥60 years)	Venlafaxine XR, titrated from 37.5 mg/day up to 300 mg/day for 12 weeks	Older adults with MDD: $N = 335$ (IRL-GREY trial)	MDD PGS was not significantly associated with remission; PGS for cardioembolic stroke was associated with nonremission (OR = 0.63, $p = 0.001$)	Vascular and neuroinflammatory genetic factors may be more influential than depression PGS in late-life antidepressant response
Monistrol-Mula *et al.*, 2024	MDD/BD PGS effects on COVID-related burnout	Cross-sectional analysis with mediation (and moderation) in AGDS	Observational study	Individuals with depression from AGDS: $N = 4405$	MDD PGS associated with higher COVID-19 burnout ($\beta = 0.36$, SE = 0.12, $p = 0.003$; top 10% vs lowest: OR = 4.17, 95% CI = 1.47–11.86); BD PGS showed a trend (highest 10% OR = 0.27, 95% CI = 0.09–0.76)	Genetic liability for depression may predispose to COVID-related burnout, an effect fully mediated by anxiety
Müller *et al.*, 2024	MDD PGS in disorder risk vs. treatment response	Secondary analysis of an 8-week treatment trial (EMC)	Initial escitalopram; switch to venlafaxine or lithium per algorithm	EMC: enrolled $N = 889$, genetic data available for 560, final analysis $N = 481$; Controls from HNR: $N = 3215$	MDD PGS associated with disorder status (Nagelkerke's $R^2 = 2.48\%$, $p < 1 \times 10^{-12}$) but ADR-PGS did not predict early improvement ($R^2 = 0.007\%$, $p = 0.879$) or remission ($R^2 = 0.194\%$, $p = 0.464$)	Common polygenic variation may influence MDD risk
Mundy *et al.*, 2024	PGS influence on treatment trajectories in early-onset MDD	Danish register-based study using latent class growth analysis over 7 years	Secondary psychiatric care for MDD (no active treatment trial)	Early-onset MDD individuals (diagnosed age 10–25): $N = 10,577$	MDD PGS was nominally associated with the later re-entry trajectory (OR = 1.09, 95% CI = 1.02–1.17, $p = 0.01$) and with continued antidepressant use (OR = 1.11, 95% CI = 1.05–1.17, $p = 0.0003$); BD PGS not significant	Genetic liability for depression may predict recurrent treatment needs in early-onset MDD
Nøhr *et al.*, 2022	PGS associations with vortioxetine/placebo response in MDD	Randomized, double-blind trials (vortioxetine $N = 907$, placebo $N = 455$) plus a 23andMe self-report sample ($N = 642$)	Vortioxetine vs. placebo	Clinical trials: $N = 1364$; additional self-reported sample: $N = 642$	No PGS reached significance after correction; nominally, PGS MDD was nominally linked to better placebo response ($\beta = 0.54$, $p = 0.011$)	Genetic predictors may differentially affect drug versus placebo response

(*continued*)

Table 1—*Continued*

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Schubert *et al.*, 2021	Combined SCZ and MDD PGS predict lithium response in BD	Cross-sectional analysis using logistic and Tobit regression	Lithium treatment; response measured by the Alda scale	Patients with BD from ConLi + Gen: $N = 2283$	PGS MDD (OR = 1.61, $p = 0.04$) predicted poorer response; combined MET2-PGS improved prediction (OR = 2.54, $p = 0.002$; Nagelkerke $R^2 = 0.91\%$)	Patients with BD with higher genetic liability for MDD are less likely to respond favorably to lithium
Sealock *et al.*, 2024	Psychiatric PGS association with antidepressant response via an EHR algorithm	Multisite EHR validation study using ordinal regression models	First antidepressant trial; response categorized as responder, intermediate, nonresponder	Data pooled from VUMC, All of Us, and MGB (sample size not specified)	Higher PGS for MDD (OR = 1.07, $p = 2.84 \times 10^{-8}$) and BD (OR = 1.04, $p = 1.99 \times 10^{-3}$) were associated with poorer response	Genetic risk for mood disorders is linked to diminished antidepressant response
Shao *et al.*, 2025	MDD PGS and clinical factors and early antidepressant efficacy	Observational study with multiple stepwise linear regression; outcome measured after 2 weeks	Antidepressant treatment; outcome: % reduction in HAM-D17 scores after 2 weeks	Patients with nonpsychotic MDD: initial $N = 999$, final $N = 912$; Han Chinese, age 18–65, baseline HAM-D17 ≥ 18	Higher MDD PGS was linked to a lower HAM-D17 reduction ($r = -0.075$, $p = 0.024$; $\beta = -4.086$, $p = 0.039$, adjusted $R^2 = 0.086$)	A higher genetic burden for depression modestly predicts reduced early antidepressant efficacy
Tansey *et al.*, 2014	BD PGS influence on antidepressant response in MDD	Meta-analysis of two cohorts (NEWMEDS: $N = 1{,}791$; STAR*D: $N = 1107$) over 12 weeks	Antidepressants: SSRIs (e.g., escitalopram, citalopram) and NRIs (e.g., nortriptyline, reboxetine)	NEWMEDS: $N = 1791$; STAR*D: $N = 1107$; patients with MDD	BD PGS explained <0.01% to 0.34% of variance in response (p values ranging from 0.829 to 0.999); no significant association was observed	Negative results in the early study may be linked to the reduced power of the origin samples
Taylor *et al.*, 2021	PGS influence on intensive inpatient TRD outcome	Observational study in a specialist inpatient service	Individualized pharmacotherapy, CBT, occupational and couples therapy, ECT if indicated	TRD patients: $N = 174$; responders = 82 (47%)	No significant associations were found between MDD PGS, BD PGS, and treatment response; clinical predictors (e.g., later age of onset) were modest (AUC < 0.6)	Genetic liability for mood disorders does not strongly influence short-term outcome in intensive inpatient treatment for TRD
Ward *et al.*, 2018	MDD and neuroticism PGS in antidepressant response	Meta-analysis across three cohorts (GENDEP $N = 267$; AMPS-1 $N = 357$; AMPS-2 $N = 138$) over 8–12 weeks	Antidepressants: escitalopram, nortriptyline, citalopram/ escitalopram	Total $N = 760$ patients with MDD	MDD PGS nominally associated with lower 4-week response ($\beta = -0.019$, $p = 0.009$) and PGS NEU nominally with lower 8-week response ($\beta = -0.017$, $p = 0.03$); variance explained was ≤1.2%	Higher genetic liability for depression and neuroticism may modestly predict poorer short-term antidepressant outcomes
Wigmore *et al.*, 2020	PGS associations with antidepressant treatment resistance in MDD	GWAS and PGS analysis; meta-analysis of GS:SFHS and GENDEP; additional GWAS on stages of resistance	Based on health service prescription data (antidepressant resistance defined via treatment stages)	Meta-analysis: $N = 4213$ (cases = 358, controls = 3855); GS:SFHS subanalysis: $n = 3452$	Antidepressant resistance was nominally associated with MDD PGS (at PT < 0.1, <0.5, <1); BD PGS was not significant	Genetic liability for MDD may contribute to antidepressant resistance
Xiong *et al.*, 2023	Lithium and antidepressant PGS in TRD MDD	Cross-sectional analysis across three Swedish cohorts (no explicit trial duration)	PREFECT: severe MDD received ECT; iCBT: mild–moderate MDD treated with internet CBT; STAGE: population MDD	Total $N = 4572$; PREFECT $N = 1{,}922$ (ECT), iCBT $N = 964$, STAGE $N = 1686$; TRD defined: broad (1778 vs 2264), narrow$_1$ (1487 vs 1483), narrow$_2$ (1081 vs. 1483)	Antidepressant response PGS showed no difference (broad diff = −0.015, $p = 0.631$); lithium response PGS was higher in TRD (broad diff = 0.094, $P = 0.003$; narrow$_1$ OR = 1.12 per SD, 95% CI = 1.04–1.20, $p = 0.003$)	TRD in MDD may be genetically predisposed to lithium responsiveness

Abbreviations: ADR, antidepressant response; BD, bipolar disorder; ECT, electroconvulsive therapy; EMC, Early Medication Change; GWAS, genome-wide association study; iCBT, internet-based cognitive behavioral therapy; MDD, major depression; NRI, norepinephrine reuptake inhibitor; PGS, polygenic score; TRD, treatment-resistant depression; R^2, coefficient of determination; RCT, randomized controlled trial; SSRIs, selective serotonin reuptake inhibitors.

report for the first time that that depression genetic liability may play a role also in the clinical evolution of eating disorders.

Nguyen *et al*. (60) then used Swedish and Danish national registries to study psychotic MDD, defined using ICD-10 subcodes F32.2/F32.3 and analyzing approximately 30,000 genotyped MDD cases from the UK Biobank and a Swedish clinical cohort. It reported that the heritability of psychotic MDD was estimated at 30.17% (95% CI = 23.53–36.80), with individuals with psychotic MDD having higher mean BD PGS [OR = 1.28, 95% CI = (1.20–1.36)], while the MDD PGS was associated with lower odds of psychotic MDD [OR = 0.93, 95% CI = (0.88–0.99)], this study is of particular interest given that it may suggest that, as expected, BD PGS may influence the risk of psychotic behavior, given its higher correlation with SCZ PGS (61, 62), while PGS MDD could define a less severe depressive subtype (31).

On the other hand, in patients with SCZ MDD PGS may have a similar effect. In fact, a study of first-episode psychosis cases examined 583 individuals from the EU-GEI study and derived transdiagnostic symptom dimensions via a bifactor model from measures such as the Positive and Negative Syndrome Scale (PANSS), finding that MDD PGS was significantly associated with lower positive [$\beta = -0.48$, 95% CI = (-0.765, -0.200), $p = 0.002$] and negative symptom scores [$\beta = -0.48$, 95% CI = (-0.754, -0.199), $p = 0.002$] but that it interacted with childhood trauma [as measured by the CTQ (Childhood Trauma Questionnaire)] to amplify positive symptoms [interaction $\beta = 0.42$, 95% CI = (0.155–0.682), $p = 0.004$], while BD PGS showed a trend toward association with lower positive symptoms [$\beta = -0.49$, 95% CI = (-0.875, -0.102), $p = 0.021$] and a significant interaction with childhood trauma on positive symptoms [$\beta = 0.45$, 95% CI = (0.106–0.798), $p = 0.010$], suggesting that genetic liability for mood disorders can influence SCZ symptomatology in a similar direction to the one observed in MDD and possibly also modulate the impact of adverse early-life experiences on psychosis symptomatology (63).

A converging evidence comes from a population study. In the Norwegian MoBa cohort, Bakken *et al*. (64) assessed 54,839 children at ages 1.5, 3, 5, and 8 years using latent growth models and latent profile analysis to characterize trajectories of emotional and behavioral difficulties, finding that the PGS for depression was significantly associated with higher baseline emotional difficulties [$\beta = 0.029$, 95% CI = (0.018–0.041), $p < 0.001$] and with a steeper increase in behavioral difficulties [$\beta = 0.041$, 95% CI = (0.024–0.058), $p < 0.001$], whereas the BD PGS was not significantly associated with overall trajectories but was specifically associated with a latent profile characterized by severe behavioral dysregulation [OR = 1.52, 95% CI = (1.21–1.90), $p = 0.001$]. This large and well powered study adds to the potentially broad effect of MDD PGS that may apply also to subjects not affected by MDD or other major psychoses.

The complex interplay with genetic liability and trauma was very recently investigated in a large study including 96,002 individuals from hospital-linked biobanks at VUMC and MGB to investigate the interaction between sexual trauma and PGSs (65). The results suggest that in individuals without sexual trauma, BD PGS was significantly associated with BD diagnosis [OR = 1.36, 95% CI = (1.31–1.42), $p < 0.002$] and MDD PGS with MDD diagnosis [OR = 1.20, 95% CI = (1.17–1.22), $p < 0.002$], while in those with documented sexual trauma, the association for BD PGS was attenuated [OR = 1.11, 95% CI = (0.99–1.23), $p = 0.072$] yet the MDD PGS association remained robust [OR = 1.21, 95% CI = (1.08–1.37), $p < 0.002$], suggesting that severe trauma may diminish the predictive power of bipolar genetic liability but not the one of depressive genetic liability, which may have a synergic contribution with trauma.

In Taiwan, Wu *et al*. (66) used data from 106,806 participants to examine associations between BD PGS with educational attainment and cognitive aging (assessed via the mini–mental state examination (MMSE) in 27,005 individuals aged ≥ 60 with longitudinal data from 6194 participants over a mean follow-up of 3.9 years), and found that BD PGS was significantly associated with higher educational attainment (OR = 1.021 per SD increase, $p = 0.001$) and that its concordant variants explained 0.48% of variance (vs. 0.39% overall), and in terms of cognitive aging, BD PGS was associated with better cognitive performance ($\beta = 0.054$, $p = 0.020$). Indeed, this study supports the complex effect of BD PGS, an effect that is not unequivocally detrimental, possibly depending on other clinical and environmental factors.

Similarly, Jiang *et al.* (67) investigated cardiovascular disease risk in 345,169 European-ancestry individuals from the UK Biobank and found that each 1-SD increase in MDD PGS was significantly associated with increased risk of atrial fibrillation [HR = 1.04, 95% CI = (1.02–1.06), $p = 1.5 \times 10^{-4}$], coronary artery disease [HR = 1.07, 95% CI = (1.04–1.11), $p = 2.6 \times 10^{-6}$], and heart failure [HR = 1.09, 95% CI = (1.06–1.13), $p = 9.7 \times 10^{-10}$] in females, whereas BD PGS showed no significant associations. This finding supports the previously discussed correlation between MDD and cardiovascular diseases, that is an area of relevant clinical and research interest.

Another piece of evidence comes from the study by Scott *et al*. (68) which examined 1473 individuals aged 15–25 from the Brisbane Longitudinal Twin Study and, through principal component analysis of four PGSs (for MDD, BD, SCZ, and NEU), derived a BD-SCZ dimension (explaining 35.7% of variance) and an MDD-NEU dimension (34.2% variance), finding that the BD-SCZ dimension was significantly higher in individuals meeting Composite International Diagnostic Interview (CIDI) criteria for a full-threshold mood or psychotic disorder ($p = 0.005$) and was significantly associated with help-seeking behavior ($p = 0.02$), while the MDD-NEU dimension was only associated with help-seeking ($p = 0.003$). One interesting aspect of this study is the further evidence of a similarity between BD and SCZ liability as well as between MDD and NEU liability while they are quite independent from each other.

An onset focused study compared 207 older adults with BD from the PsyCourse Study, distinguishing 144 early-onset BD cases (onset <50 years) from 63 late-onset cases (onset $\geq$ 50 years) (69), and found that BD PGS was significantly higher in early-onset BD ($p = 0.005$), explaining a quite relevant 6.0% of the variance (Nagelkerke's pseudo-$R^2 = 6.0\%$), whereas MDD PGS ($p = 0.66$) were not associated with age of onset. Also in this case, the small sample size may not have been powered for the low effect sizes observed in other studies.

A similar lack of effect was reported by another study, this time on neuropsychological measures (70). The study included a network analysis in 132 first-episode psychosis patients, assessing cognitive functioning and psychopathology at 2 months and 2 years, and found that no mood PGS were significantly associated with cognitive domains, but, again, the small sample size and the complex network analysis could suggest power issues.

A much larger study reported interesting findings on symptomatology (71). The study analyzed UK Biobank data from 409,630 participants for chronotype and 239,918 for insomnia, reporting that BD PGS ($p = 4.8 \times 10^{-3}$) and MDD PGS ($p = 8.07 \times 10^{-4}$) were both significantly associated with an evening chronotype, and that both BD PGS ($p = 2.9 \times 10^{-7}$) and MDD PGS ($p < 2.2 \times 10^{-16}$) were significantly associated with insomnia, suggesting that genetic liability for mood disorders contributes to symptomatology heterogeneity and circadian dysregulation. This finding is of relevant clinical interest given the known impact of circadian dysregulation in mood disorders outcome (72–75).

Harrington *et al*. (76) investigated peripartum depression in 178 parous female inpatients from an Italian sample, dividing them into MDD ($n = 72$) and BD ($n = 106$) subgroups and applying a multipolygenic risk framework with 341 PGSs, finding that both MDD and BD PGS were negatively associated with peripartum depression, though not consistently in the two subgroups. However, the relatively small sample size and the many comparisons in the study suggest caution in interpreting findings of this study.

Suicidality is another potentially interesting phenotype and it was the focus of another very recent study in 232 youth (mean age 16.7 years) with BD ($n = 125$) or at high risk for BD ($n = 107$) in Canada (77). Results suggest that MDD PGS was nominally associated with suicidal ideation ($\beta = 0.36$, SE = 0.16, $p = 0.017$; remaining significant when controlling for family history ($\beta = 0.37$, SE = 0.15, $p = 0.016$), whereas BD PGS did not significantly predict any suicidality outcomes, again suggesting a different effect of MDD genetic liability versus BD liability also on suicidal behaviors, an area that should be further investigated for its potential clinical benefit.

The different effect may reflect on the potential diagnostic power of the two PGS. In a very large study Panagiotaropoulou *et al*. (78) analyzed 51,149 individuals (15,532 BD cases, 12,920 MDD cases, and 22,697 controls) from the Psychiatric Genomics Consortium with replication in an independent iPSYCH cohort ($n = 25{,}966$, including 2524 BD and 23,442 MDD cases) to differentiate BD from MDD using genome-wide association analyses and PGS calculated with SBayesR, finding that BD PGS significantly differentiated BD from MDD (AUC = 0.62, Nagelkerke $R^2 = 2.29\%$) and that combining BD PGS, MDD PGS, and a BD versus MDD GWAS-based PGS improved classification (AUC = 0.64, $R^2 = 4.56\%$), with MDD PGS alone contributing little, thereby reinforcing that BD and MDD PGS, though correlated, have different effects. Though focusing only on diagnostic status and not on outcome, the study is interesting in further underlining the specific effects of MDD versus BD PGS.

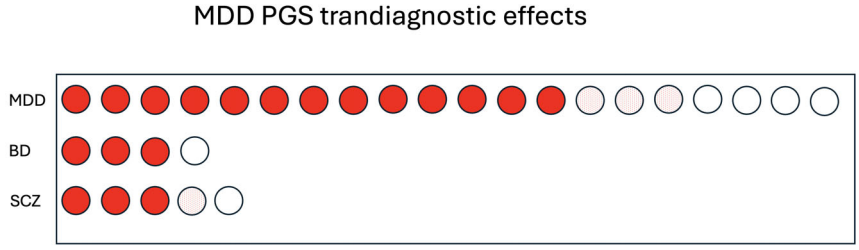

Figure 1. Visual summary of results, circles indicate independent studies on outcome or related features. Full circle: positive or nominal association, dotted circle: consistent trend, empty circle: no association. See text and tables for details.

In a similar study, Chen *et al*. (79) applied deep learning algorithms to genetic data from multiple large datasets (including MGS, SCCSS, CATIE, PGC, WTCCC, among others) to classify SCZ, BD, and MDD based on PGSs for 42 comorbid traits, and reported that for BD classification, the target BD PGS achieved an accuracy of 0.895 ± 0.020 and an AUC of 0.965 ± 0.003, while for MDD classification, the target MDD PGS achieved an AUC of 0.854 ± 0.010, with performance improving when PGSs for comorbid traits were added, suggesting that although disorder-specific polygenic risk is informative, genetic overlap with comorbid traits can further enhance diagnostic classification and possibly outcome.

Following on the possible pleiotropic effects of PGS, Segura *et al*. (80) examined the impact of PGSs on antipsychotic-induced metabolic dysregulation in a longitudinal study of 231 first-episode psychosis (FEP) patients over 6 months and found that MDD PGS, but not BD PGS were associated with total cholesterol levels (FDR = 0.006) and also at month 2 (FDR = 0.030). Though interesting, and in line with previous evidence of a correlation between metabolic and depressive backgrounds (81), also in this study the relatively small sample size suggests caution.

The complex interplay with the environment was further investigated in a study involving 573 FEP cases and 1005 controls from the EU-GEI study to investigate PGSs and environmental risk interactions (82). Results suggest that for affective psychosis, BD PGS was the strongest genetic predictor [OR = 1.50, 95% CI = (1.18–1.91), $p = 0.001$] and MDD PGS was also significant but with a smaller effect [OR = 1.34, 95% CI = (1.10–1.63), $p = 0.004$], though not interacting with environment. Therefore, whereas SCZ-spectrum disorder was primarily driven by SCZ PGS, affective psychosis may be influenced from a combination of mood disorder genetic liability and environmental factors.

Finally, Song *et al*. (83) examined 5180 BD cases from Sweden and 2577 BD cases from the UK to assess associations between BD PGS and MDD PGS with BD subphenotypes, finding that BD PGS was positively associated with full interepisode remission [OR = 1.16, 95% CI = (1.10–1.23), $p = 1.05 \times 10^{-7}$] and with higher Global Assessment of Functioning (GAF)-function scores [$\beta = 0.78$, 95% CI = (0.38–1.17), $p = 1.06 \times 10^{-4}$], and was negatively associated with comorbid anxiety disorders [OR = 0.88, 95% CI = (0.83–0.93), $p = 1.60 \times 10^{-5}$], whereas MDD PGS was negatively associated with remission [OR = 0.84, 95% CI = (0.80–0.89), $p = 2.78 \times 10^{-11}$] and GAF-function [$\beta = -0.70$, 95% CI = (−1.00 to −0.40), $p = 3.76 \times 10^{-6}$] and positively associated with comorbid anxiety [OR = 1.15, 95% CI = (1.09–1.21), $p = 8.73 \times 10^{-7}$], thus providing further evidence that MDD and BD are quite distinct polygenic liabilities that underpin different aspects of BD heterogeneity. This study is interesting also because it focuses on more detailed outcome and severity phenotypes, a much needed line of investigation, and that results further confirm the detrimental effect of MDD PGS while a mixed effect of BD PGS.

Collectively, these studies (Table 2) suggest a comprehensive picture of how PGSs for MDD and BD may influence a wide range of phenotypes that may relate to outcome: environmental exposures, symptom expression, diagnostic transitions, developmental trajectories, cognitive and educational outcomes, help-seeking behavior, treatment response itself, and even pharmacokinetic parameters, suggesting that, while higher MDD PGS is frequently associated with increased exposure to adverse events and poorer functional outcomes, BD polygenic risk exhibits a more complex pattern that can sometimes be linked to better clinical outcomes (such as higher remission rates and functioning in BD subphenotypes) and cognitive advantages, yet also modulates other aspects in a detrimental direction such as psychosis; however, the overall predictive power of these PGSs remains modest, and their clinical utility would benefit from further refinement through larger, multiancestry, longitudinal studies that integrate genetic data with environmental, clinical, and biomarker information.

Discussion

The evidence reviewed underscores both the promise and the current limitations of mood disorder PGS use in understanding the complex clinical features and treatment outcomes in major psychoses. Also, thanks to the rapid advancements in genomic discovery, due to ever-larger GWAS and more refined statistical approaches, several consistent themes emerge that clarify the clinical significance of these genetic score markers.

First, the majority of studies point to a modest but consistent relationship between MDD PGS and antidepressant treatment outcomes (Figure 1). In numerous samples, higher polygenic load for depression correlates with a greater likelihood of nonresponse, nonremission, or resistance to conventional antidepressant therapies. MDD PGS showed also a detrimental effect on BD and SCZ outcomes, this is of interest because of the transdiagnostic effect of MDD genetic liability that applies also to other diagnoses. When significant effects do arise, however, they generally explain less than 1% of variance in treatment outcomes. This small effect size highlights the persistent "missing heritability" challenge in psychiatric genomics: though large consortia have identified hundreds of common risk variants for MDD (5), they still exerts only a small influence on complex traits like symptom improvement or remission (36, 84).

By contrast, BD PGS have more variably predicted treatment outcomes (Figure 2). Some studies show little to no association with antidepressant

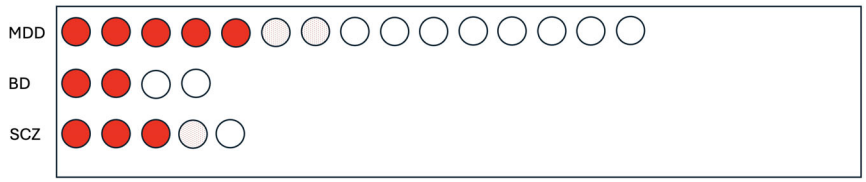

Figure 2. Visual summary of results, circles indicate independent studies on outcome or related features. Full circle: positive or nominal association, dotted circle: consistent trend, empty circle: no association. See text and tables for details.

Table 2. Summary of studies investigating MD and BD PGS and outcome-related aspects

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Abdulkadir *et al.*, 2025	ED transitions and MD/BD PGS	Registry-based analysis of Danish hospital records (1995–2018)	None	$N = 10{,}565$ individuals with eating disorders (AN = 6901; BN = 1417; EDNOS = 2247)	Higher MDD PGS associated with a 15% greater hazard of transitioning from anorexia nervosa to bulimia nervosa or EDNOS (HR = 1.15 per SD increase, $p < 1.57 \times 10^{-4}$); BD PGS was not significantly associated with diagnostic transitions.	Genetic liability for depression may influence diagnostic shifts in eating disorders
Alameda *et al.*, 2024	MD/BD PGS and childhood adversity in FEP	Cross-sectional analysis in FEP cases from the EU-GEI study	None	$N = 583$ FEP cases	MDD PGS was inversely associated with both positive and negative symptom scores ($\beta = -0.48$, $p = 0.002$) and interacted with childhood trauma (CTQ) on positive symptoms ($\beta = 0.42$, $p = 0.004$). BD PGS showed a trend for lower positive symptoms ($\beta = -0.49$, $p = 0.021$) with a significant CTQ interaction ($\beta = 0.45$, $p = 0.010$).	Genetic liability for MD and BD modulates the impact of childhood adversity on psychosis symptoms
Bakken *et al.*, 2024	Childhood trajectories and MD/BD PGS	Longitudinal analysis using latent growth models and latent profile analysis in the MoBa cohort	None	$N = 54{,}839$ children (assessed at 1.5, 3, 5, and 8 years)	PGS for depression (PGSDEP) associated with higher baseline emotional difficulties [$\beta = 0.029$, 95% CI = (0.018–0.041), $p < 0.001$] and with a steeper increase in behavioral difficulties [$\beta = 0.041$, 95% CI = (0.024–0.058), $p < 0.001$]; BD PGS was not significantly associated with trajectories.	Depression genetic liability influences early emotional and behavioral development, whereas bipolar genetic risk does not manifest in early childhood trajectories.
Chen *et al.*, 2025	Deep learning classification using MD/BD PGS	Multidataset classification using elastic net regression and deep neural networks; cross-sectional	None	Cases of schizophrenia, BD, MDD, and controls from datasets including MGS, SCCSS, CATIE, PGC, WTCCC, etc.	BD classification using BD PGS achieved accuracy = 0.895 ± 0.020 and AUC = 0.965 ± 0.003; MDD classification using MDD PGS achieved accuracy = 0.782 ± 0.015 and AUC = 0.854 ± 0.010; adding comorbid trait PGSs further improved performance.	Integrating disorder-specific and comorbid PGSs with deep learning substantially improves diagnostic classification of BD and MDD
Crouse *et al.*, 2024	Stress exposure and MD/BD PGS	Cross-sectional analysis using data from the Australian Genetics of Depression Study	None	$N = 14{,}146$ (75% female; mean age = 44.0 years, SD = 15.3); adults with depression	Higher MDD PGS associated with increased odds of childhood stressful life events (SLEs) (ORs = 1.07–1.12, p's < 0.013, FDR-corrected) and specific events [physical assault: OR = 1.06 (1.02–1.11), $p = 0.006$; sexual assault: OR = 1.10 (1.05–1.16), $p < 0.001$; severe human suffering: OR = 1.17 (1.05–1.30), $p = 0.003$]. In contrast, higher BD PGS was associated with lower odds of physical assault [OR = 0.95 (0.91–0.99), $p = 0.014$], major financial troubles [OR = 0.93 (0.88–0.98), $p = 0.004$], unpleasant surroundings [OR = 0.92 (0.87–0.98), $p = 0.008$], and fewer childhood SLEs [OR = 0.97 (0.95–0.99), $p = 0.01$].	MD genetic liability may increase exposure to stress, whereas BD genetic risk appears linked to fewer reported SLEs, challenging traditional subtype distinctions.
Fahey *et al.*, 2024	Sleep traits & MD/BD PGS	Cross-sectional analysis using UK Biobank data	None	For chronotype: N = 409,630; for insomnia: N = 239,918	BD PGS associated with an evening chronotype ($p = 4.8 \times 10^{-3}$) and with insomnia ($p = 2.9 \times 10^{-7}$); MDD PGS associated with evening chronotype ($p = 8.07 \times 10^{-4}$) and with insomnia ($p < 2.2 \times 10^{-16}$).	Shared genetic liability for mood disorders influences sleep patterns, implicating circadian dysregulation as an intermediate phenotype in psychiatric disorders.
Gil-Berrozpe *et al.*, 2025	BD/MDD PGS and cognition in FEP	Longitudinal network analysis in first-episode psychosis with assessments at 2 months and 2 years	None	$N = 132$ first-episode psychosis patients	Neither BD PGS nor MDD PGS showed associations with cognitive functioning	The small sample size and the complex network analysis could suggest power issues.
Harrington *et al.*, 2024	PPD risk and MD/BD PGS in peripartum	Cross-sectional machine-learning analysis (PLS regression) in an Italian inpatient sample	None	$N = 178$ parous female inpatients (MDD = 72; BD = 106; PPD present = 62, absent = 116)	MDD and BD PGS were negatively associated with peripartum depression	The relatively small sample size and the many comparisons in the study suggest caution

(*continued*)

Table 2—*Continued*

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Jiang *et al.*, 2024	MD/BD PGS and cardiovascular risk	Observational cohort study using UK Biobank data with replication in BioVU	None	UK Biobank: $N =$ 345,169 (European ancestry)	In females, each 1-SD increase in MDD PGS was associated with increased risk of atrial fibrillation [HR = 1.04, 95% CI = (1.02–1.06), $p = 1.5 \times 10^{-4}$], coronary artery disease [HR = 1.07, 95% CI = (1.04–1.11), $p = 2.6 \times 10^{-6}$], and heart failure [HR = 1.09, 95% CI = (1.06–1.13), $p = 9.7 \times 10^{-10}$]; BD PGS showed no significant associations.	Genetic liability for depression may elevate cardiovascular risk in females even in the absence of a clinical diagnosis
Kowalec *et al.*, 2021	TRS predictors: MD/BD PGS	Registry and genomic study in Swedish national registers	None	$N = 24{,}706$ SCZ cases (genomic subset $N = 4936$)	BD PGS, and MDD PGS were not significant, though both PGS showed a non significant trend in the direction of TRS	In treatment-resistant SCZ, familial and cognitive factors are more predictive than common MD or BD polygenic risk
Lake *et al.*, 2025	Sexual trauma and MD/BD PGS interactions	Cross-sectional analysis from hospital-linked biobanks (VUMC and MGB) with retrospective trauma data	None	$N = 96{,}002$ individuals	In individuals without sexual trauma, BD PGS was associated with BD diagnosis [OR = 1.36, 95% CI = (1.31–1.42), $p < 0.002$] and MDD PGS with MDD diagnosis [OR = 1.20, 95% CI = (1.17–1.22), $p < 0.002$]. Among those with sexual trauma, the BD PGS association was attenuated [OR = 1.11, 95% CI = (0.99–1.23), $p = 0.072$] while MDD PGS remained significant [OR = 1.21, 95% CI = (1.08–1.37), $p < 0.002$]	Sexual trauma moderates the effect of bipolar genetic risk on diagnosis, suggesting that severe environmental stress may diminish the predictive power of BD PGS, whereas MDD PGS remains robust.
Mayén-Lobo *et al.*, 2021	BD/MDD PGS and clozapine metabolism	Cross-sectional integrative genomic-epigenomic analysis in clozapine-treated refractory psychosis	Clozapine treatment	$N = 44$ patients (SCZ = 31; Schizoaffective disorder = 9; BD = 4)	BD PGS was significantly associated with clozapine metabolic ratio (pseudo-$R^2 = 0.2080$, $p = 0.0008$, adjusted $p = 0.0189$); MDD PGS was nominally associated with clozapine dose ($p = 0.0035$, adjusted $p = 0.0759$).	Bipolar genetic liability may affect clozapine metabolism and MDD PGS the prescribed dose
Montejo *et al.*, 2025	BD PGS and age of onset in BD	Cross-sectional comparison in older adult bipolar disorder from the PsyCourse Study	None	$N = 207$ older adults with BD (early-onset BD = 144; late-onset BD = 63)	BD PGS was significantly higher in early-onset BD compared to late-onset BD ($p = 0.005$), explaining 6.0% of the variance (Nagelkerke's pseudo-R^2 = 6.0%); PGS-SCZ ($p = 0.27$) and MDD PGS ($p = 0.66$) were not significantly associated with age of onset.	Higher bipolar genetic liability characterizes early-onset BD
Nguyen *et al.*, 2025	Genetic profile in psychotic depression	Population-based registry analysis using Swedish and Danish national data; PGS analysis	None	>5.1 million individuals; PGS analyses performed on ~30,000 genotyped MDD cases (from UK Biobank and a Swedish clinical cohort)	Psychotic MDD cases showed higher BD PGS (OR = 1.28, 95% CI = 1.20–1.36) but lower MDD PGS (OR = 0.93, 95% CI = 0.88–0.99) compared to nonpsychotic MDD.	Psychotic depression exhibits a distinct genetic profile, with greater overlap with bipolar liability, suggesting it is genetically less similar to typical MDD.
Panagiotaropoulou *et al.*, 2025	Differentiate BD from MDD via PGS	GWAS and PGS analysis using PGC data with replication in the iPSYCH cohort	None	PGC: $N = 51{,}149$ (BD = 15,532; MDD = 12,920; controls = 22,697); iPSYCH: $N = 25{,}966$ (BD = 2524; MDD = 23,442)	BD PGS significantly differentiated BD from MDD (AUC = 0.62, Nagelkerke's $R^2 = 2.29\%$); combining BD PGS, MDD PGS, and BD vs. MDD PGS improved classification (AUC = 0.64, $R^2 = 4.56\%$); MDD PGS alone contributed little.	BD and MDD are genetically distinct; BD-specific polygenic risk may aid in differential diagnosis
Piazza *et al.*, 2024	Depression PGS and symptom networks	Cross-sectional network analysis in two population-based cohorts (ALSPAC and TEDS)	None	ALSPAC: $N = 5521$ (mean age = 11.8 years, SD = 0.14; 50.3% female); TEDS: $N = 4625$ (mean age = 11.27 years, SD = 0.69; 53.2% female)	The depression PGS was significantly associated with the symptom "not enjoying anything" ($r = 0.04$) and with "being bullied" ($r = 0.06$) in the peer problems subscale.	Genetic risk for depression appears concentrated on specific core symptoms and environmental stressors
Rodriguez *et al.*, 2024	Genetic and environmental risk in affective psychosis	Multisite case-control study (EU-GEI) with cross-sectional PGS and environmental risk (MERS) analysis	None	$N = 573$ FEP cases and 1005 controls (European ancestry)	For affective psychosis, BD PGS [OR = 1.50, 95% CI = (1.18–1.91), $p = 0.001$] and MDD PGS [OR = 1.34, 95% CI = (1.10–1.63), $p = 0.004$] were significantly associated; no significant interaction with MERS was observed, indicating additive effects.	Affective psychosis appears to arise from a combination of bipolar and depressive genetic liability plus environmental risk

(*continued*)

Table 2—*Continued*

Study	Objective	Design	Treatment	Subjects	Findings	Implications
Scott *et al.*, 2025	PGS & help-seeking in youth mood disorders	Cross-sectional analysis from the Brisbane Longitudinal Twin Study with principal component analysis of PGS	None	N = 1473 individuals aged 15–25; 29% (n = 409) met CIDI criteria for mood/psychotic disorders; 26% (n = 388) sought professional help	A BD-SCZ dimension (explaining 35.7% variance) was significantly higher in individuals with a CIDI diagnosis (p = 0.005) and was significantly associated with help-seeking (p = 0.02); an MDD-NEU dimension (34.2% variance) was also associated with help-seeking (p = 0.003).	Genetic liability for mood disorders influences help-seeking behavior in youth
Segura *et al.*, 2022	Metabolic effects and MD/BD PGS in FEP	Longitudinal study (6-month follow-up) in first-episode psychosis patients	Antipsychotic treatment (including exposure to olanzapine/clozapine)	*N* = 231 FEP patients (baseline: 192–220; 6-month follow-up: 118–179)	Higher MDD PGS associated with increased total cholesterol over time (FDR = 0.006 overall; FDR = 0.030 at month 2); PGS-BD was not significantly associated with metabolic progression.	Depression polygenic risk may modestly influence antipsychotic-induced metabolic dysregulation, whereas bipolar genetic risk appears uninvolved.
Song *et al.*, 2024	BD subphenotypes and MD/BD PGS	Multicohort analysis in BD cases from Sweden and the UK	None	Sweden: *N* = 5180; UK: *N* = 2577 BD cases	BD PGS was positively associated with full interepisode remission [OR = 1.16, 95% CI = (1.10–1.23), $p = 1.05 \times 10^{-7}$] and higher GAF-function [β = 0.78, 95% CI = (0.38–1.17), $p = 1.06 \times 10^{-4}$], and negatively with comorbid anxiety [OR = 0.88, 95% CI = (0.83–0.93), $p = 1.60 \times 10^{-5}$]; conversely, MDD PGS was negatively associated with remission [OR = 0.84, 95% CI = (0.80–0.89), $p = 2.78 \times 10^{-11}$] and GAF-function [$\beta = -0.70$, 95% CI = (−1.00 to –0.40), $p = 3.76 \times 10^{-6}$] and positively with anxiety [OR = 1.15, 95% CI = (1.09–1.21), $p = 8.73 \times 10^{-7}$].	Different polygenic liabilities shape BD heterogeneity: BD PGS is linked to better clinical outcomes, whereas MDD PGS correlates with poorer functioning and greater anxiety
Wu *et al.*, 2024	BD PGS and education/cognition	Cross-sectional and longitudinal analysis using data from the Taiwan Biobank	None	For education: *N* = 106,806; for cognitive aging: *N* = 27,005 aged ≥ 60 (longitudinal follow-up: *n* = 6194; mean follow-up = 3.9 years)	BD PGS associated with higher educational attainment (OR = 1.021 per SD increase, *p* = 0.001) and with better cognitive performance (β = 0.054, *p* = 0.020)	Bipolar genetic liability may confer advantages in education and cognition, reflecting a complex pleiotropic influence of BD risk alleles.
Zai *et al.*, 2025	PGS and suicidality in youth BD	Cross-sectional analysis from the Centre for Youth Bipolar Disorder, Canada	None	*N* = 232 youth (mean age = 16.7; BD = 125; high risk for BD = 107)	MDD PGS was nominally associated with suicidal ideation (β = 0.36, SE = 0.16, *p* = 0.017), while BD PGS not significantly associated with any suicidality outcomes.	Depression genetic liability may contribute to suicidal ideation in youth at risk for bipolar disorder

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; AN, anorexia nervosa; AUC, area under the curve; BD, bipolar disorder; BLTS, Brisbane Longitudinal Twin Study; BN, bulimia nervosa; CI, confidence interval; CIDI, Composite International Diagnostic Interview; CNV, copy-number variant; CTQ, Childhood Trauma Questionnaire; DNN, deep neural network; ED, eating disorder; EDNOS, eating disorder not otherwise specified; FDR, false discovery rate; FEP, first-episode psychosis; GAF, global assessment of functioning; HR, hazard ratio; iPSYCH, Integrative Psychiatric Research; MD, major depressive disorder; MERS, Maudsley Environmental Risk Score; MoBa, Norwegian Mother, Father, and Child Cohort Study; OR, odds ratio; PGS, polygenic score; PPD, peripartum depression; SCZ, schizophrenia; SD, standard deviation; TEDS, Twins Early Development Study; TRS, treatment-resistant schizophrenia; URV, ultra-rare variant.

response in unipolar depression, while others suggest that BD PGS contributes to the likelihood of a favorable response to lithium in BD. Notably, multiple investigations of lithium pharmacogenetics converge on the finding that bipolar patients with lower MDD PGS are more likely to respond well to lithium. Conversely, a higher MDD PGS tends to predict less favorable outcomes under lithium treatment. These complementary patterns raise the possibility that BD is a heterogeneous construct composed of partially distinct subsamples wherein one subgroup has less polygenic liability for depression and better lithium responsiveness. This could be explained by the hypothesis that MDD PGS are indeed an indicator of higher NEU (31), therefore high MDD PGS could select a subsample of patients that are less responsive to treatment because of personality traits (85, 86). Recent approaches in detecting biotypes could further inform on those aspects (87).

A second prominent theme in the reviewed literature is the difficulty in translating these genetic markers into robust clinical tools. Even when PGS reach nominal significance, their additional explanatory power in predicting outcomes beyond conventional clinical predictors, such as baseline severity, comorbidities, or duration of illness, often remains marginal (88). Similarly, the ability of PGS to distinguish clinical phenotypes (e.g., early- vs. late-onset BD, or those with vs. without rapid cycling) is often modest, typically explaining well under 5% of variance. While these small effect sizes do not negate the scientific value of PGS, they underscore the need for polygenic information to be further improved in their predictive value and integrated into multifactorial models that also capture environmental, demographic, and biomarker data.

Third, a recurring observation is that higher MDD polygenic liability correlates with increased exposure to stressors and poorer psychosocial outcomes in both individuals with and without depression. Several studies find that participants with higher MDD PGS report more stressful life events, greater feelings of loneliness under adversity, higher incidence of cardiometabolic dysfunction, and overall poorer functional trajectories. While it may seem counterintuitive that genetic features correlate with environment, it has been clearly suggested that this may indeed be possible via specific at-risk behaviors (89). By contrast, the BD PGS often exhibits more complex or even seemingly paradoxical patterns. On

one hand, it can associate with better educational outcomes or higher cognitive functioning; on the other, it may predispose to certain affective or psychotic dimensions in specific contexts. This duality likely reflects the polygenic overlap between BD and creativity/cognition, as well as the broader pleiotropy observed for psychiatric and cognitive traits. Such evidence highlights how BD liability does not uniformly confer negative outcomes and may, in some contexts, be advantageous (90, 91). The PGS effects on stressors further complicates multivariable analyses, given the reciprocal effects, this should be taken into account when modeling the analysis.

Fourth, ancestry and sample size constraints remain major concerns. Most GWAS to date have been based on Caucasian populations, limiting the generalizability of polygenic findings. Although recent studies in Asian populations, especially Han Chinese samples, have shown broadly consistent directions of effect for MDD PGS, differences in linkage disequilibrium structure and allele frequencies may lead to attenuation of predictive power if PGS are primarily derived from European samples (46). Likewise, studies with small or heterogeneous target samples reduce statistical power and can inflate the risk of spurious findings. As the field moves forward, replication in large, multiancestry cohorts with harmonized phenotyping will be essential to refine the clinical validity of PGS. Otherwise results will be much limited in terms of model portability and prediction reliability. Recent GWAS are increasingly including other ancestries and will lead to more widely generalizable results (5).

Beyond these core themes, the reviewed studies point toward promising new directions. Efforts to integrate PGS with neurophysiological measures (e.g., EEG biomarkers) or to combine multiple PGS into meta-analytic risk profiles are providing incremental gains in predictive accuracy. Machine-learning approaches that incorporate both genetic and clinical data can, in some circumstances, yield more substantial improvements in outcome prediction compared to linear models (88, 92–94). Moreover, the discovery of gene-by-environment interactions, though so far modest, suggests that specific PGS may modulate the impact of stressors, trauma, or other risk exposures on disease severity or symptom manifestation.

Taken together, the most consistent finding is that MDD PGS may modulate both risk and outcome: it correlates with susceptibility to depression, can subtly shape treatment response and clinical features also transdiagnostically, and it seems to confer broad liability for symptomatology profile in population studies. Meanwhile, BD PGS exerts a distinctly different, and more variegated, set of influences, sometimes correlating with positive functional traits and other times associating with bipolar-specific clinical features and psychotic features. Yet in no instance has the predictive power of either MDD or BD PGS reached a threshold that would recommend immediate translation into routine psychiatric practice, though in some cases the use of extreme deciles could in a near future offer a clinically relevant prediction. Rather, these scores should be viewed as incremental predictive markers, useful in large-scale risk stratification or as part of research aimed at dissecting the heterogeneity of mood disorders and psychiatric disorders in general. Hopefully, in a near future, PGS could support clinicians in the choice of treatment, as an example with a more intensive treatment at baseline in case of negative outcome PGS prediction, at least in extreme deciles. Indeed protocols with this aim are underway (95).

Results presented in this review should be interpreted according to some limitations, the selection of the studies, though broad and performed according to convergent methods, was not following common guidelines, in order to offer a broad view of the topic. The sample size of the studies varied from small samples to large population ones, with issues on one side of adequate power and on the other of heterogeneity and poor phenotyping. Most relevant for the aim of this review is the fact that in many studies the PGS was calculated in relatively small origin GWAS samples, particularly in older studies, and this may have reduced the power of the analyses. In fact, most of the reviewed studies rely on relatively old GWAS summary statistics that are less informative in terms of explained variance when compared to the most recent studies. However in the coming years, ongoing GWAS expansions, coupled with better computational and statistical methodologies, will increase the accuracy of MDD and BD PGS thanks to the very recent large studies with public summary statistics (5, 6).

Broader ancestry representation and deeper phenotyping, incorporating longitudinal treatment response data, real-time symptom monitoring, and biological markers like inflammatory or neuroimaging signatures, could lead to a more predictive framework. Ultimately, the goal is precision psychiatry, wherein PGS could be integrated with clinical profiling to tailor interventions for each patient. While the studies synthesized here indicate that the field has taken meaningful steps toward that goal (Table 3), they also reveal how far we have to go. The modest effect sizes of current PGS demand caution, but, together with results of SCZ PGS (51), they also highlight an evolving scientific frontier that, with continued investment and methodological refinement, holds significant promise for improving care in mood and psychotic disorders.

Materials and Methods

This review synthesized evidence on the relationship between MD and BD PGS and major psychoses outcomes using a nonsystematic approach. A nonsystematic review was chosen to allow for a broad and flexible exploration of the available literature, given the heterogeneous methodologies, diverse study populations, and varying definitions of treatment response, remission, and resistance across studies. Systematic reviews require predefined inclusion criteria and structured data synthesis, which may not be suitable for topics with rapidly evolving research, methodological diversity, and studies using different polygenic scoring techniques (96). A nonsystematic approach may enable a more inclusive examination of the findings while integrating insights from various study sampling, designs and relevant phenotypes.

Study Selection

Studies were selected based on their relevance to PGS and treatment outcomes, including treatment response, remission, resistance, and disease severity. Inclusion criteria focused on original research that involved primarily adult populations diagnosed with MDD, BP, or SCZ. Nonoriginal articles, such as reviews, meta-analyses, commentaries, and editorials, were excluded, along with studies that did not explicitly assess disease outcomes in relation to PGS.

Search Strategy

A targeted literature search was conducted using PubMed and Google Scholar, employing a range of relevant keywords and search terms related to PGSs and psychiatric disorders. These included:

> "polygenic score", "PGS", "risk profile score", "genetic risk score", "genetic score", "polygenic", "depression", "mood", "schizophrenia", "antidepress", "treatment resistance", "bipolar", "BP", "BD", "treatment outcome", "antipsycho*", "stabiliz*", and "remission"*, in various combinations.

To ensure comprehensive coverage, additional studies were identified through citation tracking, including forward citation searches (examining studies that have cited key papers) and backward citation searches (reviewing references cited within relevant articles). Studies known to the authors or cited in prior literature reviews were also considered when relevant. Given the pleiotropy of the genetic factors and the complex interplay of clinical and environmental factors, relevance of the selected papers was based on the previously defined outcomes and possible outcome-related phenotypes.

Data Extraction and Synthesis

Extracted data included: Sample size, population characteristics (e.g., diagnosis, demographic details), definitions of treatment outcomes (response, remission, resistance, and severity), PGS calculation methods, statistical results (associations between PGS and psychiatric outcomes). Given the heterogeneity in study methodologies, including differences in PGS computation, sample populations, outcome definitions, and statistical approaches, a meta-analytic approach was not feasible. Instead, findings were synthesized narratively, summarizing trends and highlighting key associations between PGS and psychiatric treatment outcomes and relevant phenotypes.

Table 3. Results summary

Focus/Phenotype	MDD PGS	BD PGS
Antidepressant response	• Consistently shows modest but significant correlations with poorer outcomes (lower remission, higher risk of nonresponse or TRD).	• No strong link to MDD antidepressant response.
Treatment-resistant depression (TRD)	• Frequently associated with TRD, though not always surviving strict multiple testing corrections.	• No consistent or notable association with TRD.
Lithium response in bipolar disorder	• In BD cohorts, higher MDD PGS → poorer lithium response.	• BD PGS alone sometimes shows a positive (or neutral) link to lithium response, but is less consistent than MDD or SCZ PGS.
Bipolar course and subtypes	• Within BD, higher MDD PGS often predicts more depressive episodes, poorer remission, and increased anxiety.	• BD PGS can be linked to better overall functioning or remission in BD, but also sometimes to psychotic/affective features.
SCZ/psychosis dimensions	• In first-episode psychosis, higher MDD PGS can correspond to lower "core psychosis" severity but might exacerbate affective or stress-related symptoms.	• BD PGS shows a somewhat similar pattern of reducing core psychosis but interacting with adversity to worsen positive symptoms.
Environmental and stress interactions	• Higher MDD PGS correlates with increased exposure to life stress and heightened susceptibility to negative emotional outcomes in stressful settings.	• BD PGS has shown weaker or inconsistent G × E interactions compared to MDD PGS.
Comorbidities and functional traits	• Linked to higher rates of cardiometabolic risk, suicidality, or anxiety. • Can heighten the likelihood of a "switch" to more severe conditions (e.g., from anorexia to bulimia).	• Often associated with higher educational attainment or better cognition in some populations, but also with risk of mania or psychotic features in others. • High BD PGS in BD populations linked to better remission and functioning.
Overall effect sizes and clinical utility	• MDD PGS consistently shows a subtle negative impact on depression outcomes but rarely exceeds 1% in variance explained.	• BD PGS alone does not strongly predict MDD outcomes, but in BD it can contribute to lithium response, remission, and subtypes.

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