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Research Articles

Polygenic scores and antidepressant treatment outcomes in major depression: a critical integrative review

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ABSTRACT

Major depressive disorder (MDD) shows a large heterogeneity in antidepressant treatment outcome, a variability explained in part by common-variant liability captured by polygenic scores (PGSs). We performed a review of PubMed- and Google Scholar-indexed studies that related any PGS to treatment response, remission or resistance in adult MDD.

Thirty-nine investigations met inclusion criteria. MDD-PGS emerged as the most consistently replicated predictor, each standard deviation increase raising non-remission odds by ~10–14 % across six European trials and two biobank analyses. Schizophrenia genetic liability (SCZ-PGS) was uniformly detrimental under monoaminergic monotherapy (OR~2.2 for top quintile) while possibly associated with improvement to electroconvulsive therapy (ECT) or lithium augmentation. Bipolar disorder PGS predicted faster lithium response (HR~1.5), while attention-deficit/hyperactivity-disorder PGS was reliably associated with treatment-resistant depression (TRD) in multiple studies. PGSs for coronary-artery disease and stroke similarly reduced antidepressant efficacy and doubled TRD odds.

Across traits, individual PGSs generally explained <1 % of outcome variance, but multi-omic models integrating pharmacokinetic alleles, inflammatory markers and clinical covariates reached 8–12 %. Methodological barriers include ancestry bias (>85 % European), heterogeneous phenotyping and small discovery cohorts. Even so, PGSs may support pathway-specific treatment modifiers and justify prospective trials of genotype-guided lithium, ECT or augmentation with drugs modulating inflammation-metabolism. Scalable precision psychiatry will require multi-ancestry discovery, harmonised longitudinal outcomes and equitable implementation frameworks, but current evidence signals a realistic path from genomic insight to stratified care.

1. Introduction

Major depressive disorder (MDD) remains one of the leading contributors to years lived with disability worldwide, affecting more than 280 million people in 2019 alone (GBD, 2019 Mental Disorders Collaborators, 2022). Although pharmacotherapy is effective, therapeutic success is still partial: in the STAR*D trial only ~37 % of patients remitted after their first selective-serotonin-reuptake-inhibitor (SSRI) trial and cumulative remission plateaued below 70 % even after four sequential steps (Rush et al., 2006; Warden et al., 2007).

Twin-meta-analysis places the narrow-sense heritability of MDD at ~37 % (Sullivan et al., 2000), underscoring a substantial, but polygenic, genetic contribution. Early candidate-gene efforts proved irreproducible when examined in large datasets, highlighting the danger of small

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samples and publication bias (Border et al., 2019). Consequently, the field focused on genome-wide association studies (GWAS), which, through ever-larger consortia, have mapped an increasingly complex genetic architecture, identifying 44 risk loci in 2018 (Wray et al., 2018), 102 independent loci in 2019 (Howard et al., 2019) and the most large and recent GWAS identified 308 high confidence loci (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2025).

Polygenic scores (PGS, also termed polygenic risk scores, PRS) summarise the effect of many common variants across the genome into a single quantitative index of genetic liability to a trait (Murray et al., 2021). We preferentially use the neutral term PGS rather than PRS to reflect that such scores capture the full spectrum of liability, including both risk-increasing and potentially protective alleles, rather than deterministic 'risk' alone. Conceptually simple yet statistically powerful, PGSs test whether the shared additive genetic burden that predisposes to MDD (or to other traits) also modulates treatment outcome. Their potential clinical utility has been reviewed extensively, most recently by Lewis and Vassos, who argued that psychiatry is "on the road from discovery to implementation" but still hampered by modest predictive power and ancestry gaps (Lewis and Vassos, 2022).

Empirical evidence is however rapidly accumulating. A 2022 systematic review catalogued 30 separate traits whose PGSs had been investigated for association with antidepressant response; notable association signals included PGSs for attention-deficit/hyperactivity disorder (ADHD), openness, coronary artery disease (CAD) and stroke (Meerman et al., 2022). Complementing that work, a broader psychiatric pharmacogenomics review reported that, across 53 primary studies, most PGSs alone explained ≤ 5 % of outcome variance, but their performance improved when integrated with clinical variables (Sharew et al., 2024). In the following years, large-scale primary analyses have begun to validate these signals. We showed that a higher MDD-PGS increased the odds of non-remission by ~14 % in a six-cohort meta--analysis (Fanelli et al., 2022), while the largest genome-wide association study (GWAS) of prospectively assessed antidepressant response (n ~ 5800) demonstrated for the first time a genome-wide SNP-heritability for remission ($h^2 \sim 0.13$) and significant negative genetic association with schizophrenia and educational attainment (EA) (Pain et al., 2022). Together with biobank-scale electronic health record studies reporting concordant effect sizes (Xiong et al., 2025; Coombes et al., 2024), recent data further support the evidence that polygenic liability, though individually small, exerts measurable influence on pharmacological outcome.

Yet, translational limitations remain. Effect sizes are modest, ancestry representation is heavily European, and outcome definitions (e.g., response, remission, resistance, persistence of symptoms) as well as base GWASs and methodology used for PGS computation vary across studies, limiting the possibility of meta-analytic synthesis. Moreover, pleiotropy means that PGSs derived from mechanistically distant traits (e.g., coronary-artery-disease, C-reactive-protein, educational attainment) can outperform MDD-PGS itself in certain contexts, complicating biological interpretation. As emphasised by recent position papers, clinical application will require richer models that integrate PGSs with pharmacokinetic variants and other -omic variables, environmental exposures, and longitudinal clinical data (Lewis and Vassos, 2022; Comai et al., 2025).

The present review aims therefore to provide an up-to-date synthesis of how PGSs for psychiatric and other traits relate to antidepressant treatment outcomes in adult MDD. By reviewing the evidence across heterogeneous methodologies and outcome definitions, we seek to (i) clarify which signals are most robust, (ii) identify sources of inconsistency, and (iii) outline methodological recommendations for the next generation of predictive models.

2. Methods

The present paper synthesized evidence on the relationship between PGSs and treatment outcomes in MDD using a narrative approach. A non-systematic review was chosen to allow for a more broad and flexible analysis of the available literature, given the heterogeneous methodologies, study populations, and varying definitions of treatment outcome across studies (OSF number: osf.io/x5rjh). Systematic reviews are powerful tools, but they 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 (Teixeira da Silva and Daly, 2024). A rigorously structured, though non-systematic approach may allow a more inclusive and complete examination of the relevant findings while integrating insights from various study sampling, designs and relevant phenotypes.

2.1. Study selection

Studies were selected based on their relevance to PGSs and treatment outcomes. Inclusion criteria focused on original research that involved primarily adult populations diagnosed with MDD. Non-original articles, such as reviews, meta-analyses, commentaries, and editorials, were excluded, along with studies that did not explicitly assess outcomes in relation to PGS.

2.2. Search strategy

A targeted literature search was conducted using PubMed and Google Scholar, employing a range of relevant keywords and search terms related to polygenic scores and psychiatric disorders: (("polygenic risk score"[Title/Abstract] OR "polygenic score"[Title/Abstract] OR PGS [Title/Abstract] OR PRS[Title/Abstract]) AND (antidepressant*[Title/Abstract] OR SSRI[Title/Abstract] OR SNRI[Title/Abstract] OR TCA [Title/Abstract] OR MAOI[Title/Abstract] OR esketamine[Title/Abstract] OR ketamine[Title/Abstract] OR rTMS[Title/Abstract] OR "transcranial magnetic stimulation"[Title/Abstract] OR ECT[Title/Abstract] OR "electroconvulsive therapy"[Title/Abstract] OR psychotherap*[Title/Abstract] OR CBT[Title/Abstract] OR ICBT[Title/Abstract]) AND (response[Title/Abstract] OR remission[Title/Abstract] OR resistance[Title/Abstract] OR outcome[Title/Abstract] OR "treatment resistant"[Title/Abstract])) NOT (child*[Title/Abstract] OR adolescen*[Title/Abstract]) AND ("2021/04/13"[PDAT]: "3000"[PDAT]).

To ensure comprehensive coverage, additional studies were identified through citation tracking, including forward and backward citation searches. 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.

2.3. Data extraction and synthesis

Extracted data included: Sample size, population characteristics, treatments, definitions of treatment outcomes, base traits used for PGS computation, results. 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 by summarising and highlighting associations between PGS and treatment outcomes.

3. Results

3.1. MDD PGS

Replicated evidence supports that polygenic liability for MDD

modulates antidepressant efficacy, though not confirmed by all studies and still clinically modest (Table 1). The most relevant finding comes from a meta-analysis of six European trials (N ~ 3600) (Fanelli et al., 2022). Using the largest available external MDD GWAS as the discovery panel at that time (Howard et al., 2019), the study showed that each standard deviation (SD) rise in standardised MDD-PGS raised the odds of failing to reach symptom remission by 14 % (OR = 1.14, p = 0.004) and of failing to respond by 10 % (OR = 1.10, p = 0.013). Although the pseudo-R^2 was only 0.24–0.57 %, the direction was identical in every cohort (I^2 = 0 %). Two large electronic-health-record (EHR) studies confirmed the signal: one study analysed >30,000 genotyped patients in BioVU and Mass-General Brigham and found an OR = 1.11 per SD for moving one step toward non-response on a four-level outcome (Sealock et al., 2024), whereas another study used self-report data from 19,516 UK Biobank (UKB) participants and obtained an OR = 1.08 for SSRI non-response after stringent Bonferroni correction (Kamp et al., 2025). Using UKB primary-care records to define seven proxies of treatment-resistant depression (TRD) (Wang et al., 2025), the two broadest phenotypes (medication switching and three-drug use) were associated with MDD-PGS with an ORs of 1.07; though another study in UKB showed a similar effect size, it was not significant after Bonferroni correction (Fabbri et al., 2021). Earlier studies did not find associations between treatment outcomes in MDD and MDD-PGS in smaller samples (García-González et al., 2017; Fanelli et al., 2021; Tansey et al., 2014; Ward et al., 2018), but they used base GWAS that were a fraction of recent studies and had heterogeneous phenotypes.

Mixed findings were reported for outcomes of electroconvulsive-therapy (ECT). In the nationwide Swedish ECT register (N = 2320), higher MDD-PGS predicted worse outcome (OR ~ 0.85 for remission) (Sigström et al., 2022), whereas in a smaller Irish–Belgian–Dutch sample of N = 266 no effect was observed, probably because of a power issue (Luykx et al., 2022). The most recent and largest study combined register-linked cohorts from Sweden, the Estonian Biobank and Finn-Gen, yielding 2062 electroconvulsive-therapy-defined TRD cases, 441, 037 healthy controls, and 38,544 non-TRD MDD cases (Xiong et al., 2025); the largest sample was the one from Sweden (1487 TRD, 1483 non-TRD and 5417 controls), therefore this was used to estimate TRD SNP-heritability. TRD was defined as ≥1 adequate antidepressant treatment (>6 weeks) preceding ECT, whereas non-TRD as no ECT, ≤2 adequate pharmacological treatments and excluded lifetime schizophrenia, schizo-affective or bipolar; controls had no lifetime MDD. SNP-heritability, estimated in the Swedish subset, was 26 % on the liability scale for TRD versus controls (95 % CI 16–37 %, $P = 1.3 \times 10^{-6}$) and 20 % for TRD versus non-TRD but the latter was not significantly different from zero (95 % CI –5 – 45 %, P = 0.122). The GWAS meta-analysis (~7M SNPs) identified one genome-wide-significant signal in SPATA16 for TRD risk (rs57609176, $P = 3.582 \times 10^{-8}$). Genetic correlation analyses showed high positive overlap of TRD (vs controls) with bipolar disorder (rg = 0.86, SE = 0.20) and schizophrenia (rg = 0.57, SE = 0.13), and a negative correlation with intelligence (rg = −0.13, SE = 0.07). PGS analyses demonstrated robust associations between several PGSs and TRD vs controls, with OR 1.53 (95 % CI 1.46–1.61) per SD increase in MDD PGS (), OR 1.47 (95 % CI 1.40–1.55) for BD PGS () and OR 1.35 (95 % CI 1.29–1.42) for SCZ PGS()TRD vs non-TRD MDD status was most strongly predicted by the BD PGS (OR 1.26, 95 % CI 1.19–1.33), followed by the MDD PGS (OR 1.11, 95 % CI 1.05–1.17), whereas intelligence PGS was inversely associated (OR 0.94, 95 % CI 0.88–0.99). Rare-variant analyses in the Swedish sample revealed a higher burden of large deletions: each additional 100 kb of deletion length conferred OR 1.02–1.03 for TRD versus controls (P_emp = 0.002–0.006) and OR 1.03–1.04 versus non-TRD (P_emp = 0.009–0.031) carrying any of 54 established neuropsychiatric CNVs increased odds of TRD (OR 1.74 vs controls; OR 2.86 vs non-TRD), with the 16p12.1 deletion showing a nominal association (OR 3.62, 95 % CI 1.26–10.40).

In conclusion, MDD-PGS was consistently associated with antidepressant outcomes including TRD by several studies, despite some negative studies and the low variance explained, namely < 1 % of variance in the best powered settings. An additional limitation is that most cohorts pooled outcomes across pharmacological classes, combining SSRIs, SNRIs, TCAs and even augmentation strategies into single response variables. This approach increases statistical power but inevitably blurs drug-specific mechanisms, for instance serotonergic versus noradrenergic versus glutamatergic modulation, which may interact differentially with polygenic liabilities. Such heterogeneity likely attenuates detectable effects and conceals subtype-specific associations.

3.2. SCZ PGS

The evidence supporting an effect of schizophrenia PGS (SCZ-PGS) on treatment outcomes in MDD is more consistent than other PGS, and mechanistically intriguing, as we will discuss later (Serretti and Baune, 2025). All large pharmacological studies reported that higher SCZ-PGS was associated with poorer treatment outcomes. The European Group for the Study of Resistant Depression (N = 1148) reported that patients in the highest SCZ-PGS quintile had more than twice the risk of non-response (OR = 2.23) (Fanelli et al., 2021). A large GWAS meta-analysis of clinical trials found a significant negative genetic covariance between antidepressant remission/improvement and schizophrenia, indicating that variants lowering schizophrenia risk also favour better treatment outcomes (Pain et al., 2022). Following studies using proxy phenotypes including TRD derived from biobank data replicated the association in large and diverse samples, with OR = 1.06–1.08 (Sealock et al., 2024; Wang et al., 2025), including a recent analysis on UKB self-reported antidepressant response (OR = 1.06) (Kamp et al., 2025) and the previously mentioned large population study (Xiong et al., 2025). However, the direction of association reverses in a relatively small study (n = 266) that considered response to ECT (Luykx et al., 2022). In this study, each SD increase in SCZ-PGS enhanced symptom change by 0.54 HDRS points (R^2 ~ 7 %), the largest variance explained by any single PGS in the field; however, the relatively small sample size should be taken into account, as this estimate may be unstable and not replicable in independent samples. In psychotic-depression treated with sertraline + olanzapine (Men et al., 2023) there was no association with SCZ-PGS, and vortioxetine trials (Nøhr et al., 2022) found no effect either, but self-reported vortioxetine outcome in 23andMe (N = 742) showed a strong negative association with SCZ-PGS (β = −0.28).

A possible interpretation of these findings is that SCZ-PGS indexes a psychosis liability that undermines the effects of serotonergic pharmacological treatments, but may still respond to ECT or augmentation treatments, e.g., with atypical antipsychotics.

3.3. BD PGS

Bipolar disorder PGS (BD-PGS) is less clearly associated with SSRI outcomes, suggesting that BD liability is not a primary genetic factor involved in non-response to first line MDD treatments. However, in a prospective cohort treated with lithium-augmentation (N = 193) (Kraft et al., 2025), one-SD increase in BD-PGS improved both response (HR = 1.29) and remission (HR = 1.52), with Nagelkerke R^2 up to 4.5 %. Sensitivity analyses with a different method for PGS calculation and a broader sample (N = 286) replicated the effect. Similar findings were reported in the Swedish ECT registry, where BD-PGS improved both CGI-I and MADRS-S outcomes (Sigström et al., 2022). However, the previously mentioned large population study using an ECT-based definition of TRD reported an association in the opposite direction (Xiong et al., 2025). BD-PGS was associated with lithium, valproate or antipsychotic augmentation in UKB primary-care data, and with ECT treatment (Wang et al., 2025), with per-PGS SD ORs reaching 1.45 for lithium augmentation in patients with history of hospitalisation. Early

Table 1
Summary of studies investigating associations between PGSs and depression treatment outcomes.

Study	Sample	Examined PGS	Treatment	Endpoint	Main findings
Antidepressant Medications					
Amare et al., 2018	PGRN-AMPS MDD = 529 + ISPC MDD = 865; Total = 1394	Big-Five personality traits: openness, conscientiousness, NEU, agreeableness, extraversion	SSRIs (escitalopram/citalopram/others)	Response & remission at 4/8 wk (QIDS-C16, HRSD-17)	Openness PGS predicted poorer 4-wk response (ISPC quartile Q4 vs Q1: OR = 0.30 95 %CI = 0.15–0.59; R^2 ~ 1.5 %) and remission (PGRN-AMPS Q4 vs Q1: OR = 0.4; R2 ~2.8 %); conscientiousness & neuroticism nominal; others null
Amare et al., 2019	ISPC MDD = 865 + STAR*D MDD = 1878; Total = 2743	CAD, Obesity	SSRIs	Response at 4 wk (HRSD-17 OR = QIDS-C16)	CAD-PGS predicted poorer response (ISPC Q4 vs Q1: OR = 0.53 95 %CI = 0.35–0.81); Obesity-PGS similar (OR = 0.53 95 %CI = 0.32–0.88); variance ≤ 1.3 %
Coombes et al., 2024	MCB 12558; BioMe 8206	Depression, chronic-pain, addiction, smoking, etc.	ADs (EHR)	# unique ADs prescribed	Depression-PGS & chronic pain-PGS $p < 0.0029$; $\Delta R^2 \leq 2.5$ %; more polygenic burden → more AD trials
Elsheikh et al., 2024	IRL-GRey MDD = 342 (remitters 175)	ADHD, BD, intelligence, etc.	Venlafaxine XR	Remission & %-improvement at 12 wk	ADHD-PGS OR = 1.36 95 %CI = 1.073–1.730, p = 0.011; β −5.07 ± 1.97 %, p = 0.011; not Nyholt-significant
Fabbri et al., 2021	UKB TRD = 2165 vs non-TRD = 14207	ADHD, MDD, SCZ, BD	ADs (primary care)	TRD (≥ 2 switches)	ADHD-PGS OR = 1.09 95.%CI = 1.04–1.14, $p < 0.001$ after Bonferroni; other PGS ns
Fanelli et al., 2021	GSRD MDD = 1148 (responders 279; non-responders 390; TRD 479)	SCZ, MDD, BD, NEU	Mixed ADs	Response vs non-response (≥ 50 % Δ)	SCZ-PGS PT 0.10: highest quintile OR = 2.23 95.%CI = 1.21–4.10, p = 0.02 (nominal); none survived correction
Fanelli et al., 2022	6 cohorts; responders = 1 550, non-responders = 2087; remitters = 1085, non-remitters = 2099	MDD, SCZ, BD, NEU	Mixed ADs	Non-response/non-remission (4–12 wk)	MDD-PGS: OR = 1.14 95 %CI = 1.04–1.24, p = 0.004; SCZ-PGS OR = 1.16 95 %CI = 1.01–1.33, p = 0.035; none Bonferroni-significant
Fanelli et al., 2025	UK Biobank MDD = 30,919 (IR^+ = 16063 with ≥1 insulin-resistance–related diagnosis)	Ten IR-related traits (BMI, CAD, T2D, FPG, 2 h-glucose, HbA1c, HDL, HOMA-IR, LDL, TG)	Mixed ADs (primary-care EHR)	Non-response (≥ 1 switch), TRD (≥ 2 switches), cumulative treatment time (proxy for chronicity)	No PGS survived Bonferroni α = 0.0006; CAD-PGS nominally associated with TRD, CAD and HDL PGSs with overall treatment time; FPG and TG PGSs with TRD when MDD preceded IR onset; BMI PGS with TRD and TG PGS with both TRD and longer treatment when IR onset preceded MDD (all $R^2 \leq 3.9$ %).
García-González et al., 2017	7 cohorts, N = 3746	Study-derived PGS, MDD, SCZ	SSRIs/SNRIs	Remission (6–12 wk)	Cross-study PGS p = 0.024 (R^2 0.00044); no result met Bonferroni; MDD/SCZ PGS ns
Kamp = et al., 2025	UK Biobank SSRI users N = 19516 (citalopram 8335; fluoxetine 8476; paroxetine 2297; sertraline 5883; lifetime MDD)	Depression, ADHD, ASD, BD, SCZ, two AD-response traits	SSRIs (self-reported use)	"Did this SSRI help = you feel better?" (Yes/No, lifetime)	Depression-PGS predicted non-response (OR = 1.08, $p = 3.37 \times 10^{-5}$); ADHD- and Autism-PGS nominal (OR~ 1.06); AD-response PGSs not significant; ΔR^2 for depression PGS ~ 0.3 %.
Kraft et al., 2025	Unipolar MDD = 193 (lithium augmentation)	BD, MDD, SCZ	Lithium add-on	Time to response & remission	BD-PGS HR 1.52 95 %CI = 1.14–2.04 p = 0.004 (remission); MDD-PGS HR 0.81 p = 0.048 (response)
Li et al., 2020	Esketamine TRD = 527	15 traits (e.g., depressive-symptoms)	Esketamine	% MADRS change; response; remission (4 wk)	Depressive symptoms PGS β -3.06 ± 0.94, $p = 1.20 \times 10^{-3}$; OR = 1.54 p = 0.004; none $p < 0.0004$
Liu et al., 2024	Perinatal antidepressant users = 2316 pregnancies	MDD, BD, SCZ	AD use patterns	Trajectory class (continuers, early/late discontinue, interrupters)	No PGS association (all RR ~ 1.0; 95 %CI = span 1)
Lo et al., 2025	UKB SSRI users = 38,813 (switchers 5133) + GS replication 1777	AD-non remission, MDD, SCZ	SSRIs	Switch to new AD considering ≤90-day gap between prescriptions in primary care	AD-non remission PGS OR = 1.07 p = 0.007 (≥ 2 MDD codes); MDD & SCZ PGS ns
Magarbeh et al., 2025	CAN-BIND-1 MDD = 148 (week 8)/136 (week 16)	MDD, PTSD, SCZ, ADHD, BD, NEU, Anxiety, SUD, AD-%-improvement/non-remission	Escitalopram ± aripiprazole	Remission & % change in MADRS (symptom improvement) at 8 & 16 wk	At wk 8: PTSD and MDD-PGS nominally associated with decreased remission, anxiety PGS with increased % change, and PTSD PGS with reduced %

(*continued on next page*)

Table 1 (*continued*)

Study	Sample	Examined PGS	Treatment	Endpoint	Main findings
					change; at wk 16: MDD-PGS nominally associated with remission and increased % change, ADHD PGS with reduced % change; none met $p < 0.0013$
Markant et al., 2025	Swedish twins = 2515 (AD monotherapy 555 vs multitherapy 1478)	42 traits (notable ADHD, depression, EA, asthma, addiction, personality and well-being traits)	ADs	AD monotherapy (=response) vs multitherapy status (=nonresponse)	Nominal association between ADHD-PGS and nonresponse (OR = 1.13, p = 0.014, FDR 0.086); depression-PGS significantly associated with nonresponse in females only (OR = 1.20, p = 0.004, FDR 0.042)
Marshe et al., 2021	Late-life MDD ≥ 60 y, N = 307	Cardioembolic-stroke	Venlafaxine XR	Remission MADRS ≤ 10 at 12 wk	1 SD PGS increase → OR = 0.63 95 %CI = 0.48–0.83, p = 0.001; adj R^2 0.046
Men et al., 2023	Psychotic-MDD N = 143 Europeans	AD-improvement, Alzheimer's disease	Sertraline + olanzapine	Remission ≤ 12 wk; relapse 36 wk	AD-improvement PGS OR = 1.95 p = 0.007 (remission); Alzheimer PGS OR = 0.006 p = 0.002 (relapse); none Bonferroni-sig
Müller et al., 2024	EMC MDD = 481	MDD, AD-response	Escitalopram algorithm	Early improvement (14 d); response (28 d); remission (8 wk)	No association (all p > 0.46; $NkR^2 \leq 0.256$ %)
Mundy et al., 2024	Early-onset MDD = 10577 (4 trajectory classes)	MDD, ADHD, ASD, AN, SCZ	Secondary-care contact & AD Rx	7-yr treatment-trajectory class	ADHD-PGS OR = 0.91 95 %CI = 0.87–0.96, p = 0.0002 (prolonged vs brief); AN-PGS OR = 1.12 95 %CI = 1.03–1.21, p = 0.005 (persistent)
Nøhr et al., 2022	Vortioxetine trial N = 1364 (drug 907; placebo 455) + 23andMe N = 742	AD-response, MDD, SCZ, etc.	Vortioxetine/placebo	Multiple scales 6–8 wk	Self-report cohort: SCZ-PGS β −0.283 ± 0.058, p = 0.0001 (Bonferroni-sig); clinical sample ns
Nuñez et al., 2024	BD N = 861 (TEM 313)	AD-response	AD exposure	TEM (≤ 8 wk)	AD-response PGS OR = 1.27 p = 0.011 in BD-I; no effect BD-II
Pain et al., 2022	Discovery MDD = 5218; 5 prospective cohorts fOR = replication	Remission & %-improvement	Multiple ADs	Remission/ %-improvement (≤ 12 wk)	Leave-one-out $R^2 \sim 0.1$ %; external remission PGS R^2 0.8 % (p = 0.015); effect modest but replicable
Paolini et al., 2025	MDD N = 165 (genotyped 113; TRD vs non-TRD)	7 CV-risk traits	Mixed ADs	TRD (≥ 2 failed trials)	Cardiovascular PGS PGS002535 OR = 2.22 p = 0.015; WMH mediates via β 0.25 p = 0.002
Sealock et al., 2024	BioVU + MGB N ~30152 Europeans	MDD, SCZ, BD, anxiety, cross-disorder	First-trial AD	4-level ordinal outcome	MDD-PGS OR = 1.11 $p = 5.09 \times 10^{-18}$; SCZ-PGS OR = 1.06 $p = 7.5 \times 10^{-7}$; BD-PGS OR = 1.06 $p = 8.15 \times 10^{-7}$
Shao et al., 2025	Han-Chinese MDD = 912	MDD, SCZ	Various ADs	% $HAM\text{-}D_{17}$ reduction at 2 wk	High MDD-PGS (PT 0.05) β −4.086 SE 1.975 p = 0.039; Mann–Whitney p = 0.009; SCZ-PGS ns
Tansey et al., 2014	NEWMEDS MDD = 1790 (SSRI = 1222; NRI = 568) + STAR*D MDD = 1107	BD	SSRIs, NRIs	Symptom-% change ≤ 12 wk (primary trial scales)	No association at any threshold (all $R^2 \leq 0.0034$; P ≥ 0.168)
Wang et al., 2025	UKB MDD = 15125 (multiple TRDp = proxies)	MDD, ADHD, BD, SCZ, alcohol	AD switches, augmentation, ECT	Seven TRDp = definitions	BD-PGS strongest: OR = 1.45 $p = 2.9 \times 10^{-7}$ for lithium augmentation; MDD/ADHD/SCZ PGS OR = 1.07–1.16 across proxies
Ward et al., 2018	AMPS-1 499, AMPS-2 229, GENDEP = 267; total 760	MDD, NEU	Citalopram/ escitalopram	% symptom change at 4 & 8 wk	MDD-PGS β −0.020 p = 0.009 (4 wk); NEU-PGS β −0.017 p = 0.030 (8 wk); not corrected
Wigmore et al., 2020	GS:SFHS + GENDEP=N = 4213 (TRD 358)	MDD, SCZ, BD	Community ADs	TRD (≥ 2 switches) & stages	MDD-PGS β 0.012 p = 0.012; SCZ-PGS β 0.011 p = 0.027; neither passed FDR
Xu et al., 2025	Genotyped = 292663; discovery WGS-European non-MDD = 104128, trMDD = 16640, TRD = 4177	61 traits including EA, Intelligence, Insomnia, NEU, depressive-affect subtraits (tenseness, unenthusiasm, depressed mood, lethargy)	Real-world AD prescribing (All of Us study); TRD defined as ≥3 distinct drugs in one episode	TRD vs trMDD status from EHR; mean follow-up 944 days (95 % CI 883–992)	11 PGSs belonging to the education/cognition, sleep, personality, and temperament domains associated with TRD vs trMDD, including Education and Intelligence PGSs (protective); Insomnia, NEU, Tenseness, Unenthusiasm, Depressed mood, and Lethargy PGSs (increase TRD risk)
Zwicker et al., 2018	GENDEP MDD = 755 (escitalopram = 432; nortriptyline = 323)	CRP	Escitalopram vs nortriptyline	MADRS change to 12 wk	Drug × CRP-PGS interaction significant at PT 0.20 (β = 1.07 95 %CI = 0.26–1.88, p = 0.009):

(*continued on next page*)

Table 1 (*continued*)

Study	Sample	Examined PGS	Treatment	Endpoint	Main findings
					higher PGS → better escitalopram, worse nortriptyline outcome
Other Treatments					
Bäckman et al., 2025	ICBT cohort = 2668	EA, IQ, ADHD, ASD, BD, MDD, SCZ, cross-disorder psychopathology	12-wk ICBT	Weekly slope of symptom score	EA-PGS main effect β = −0.69 p = 0.04 and time interaction β = 0.07 p~ 0.045; others ns
Kravchenko et al., 2025	ICBT depression/anxiety = 2668	MDD, ADHD, ASD, BD, SCZ, IQ, EA	12-wk ICBT	Post-treatment severity	No PGS significant (all p > 0.09); adding PGS raised adj R^2 by 0.2 pp
Luykx et al., 2022	ECT MDE = 266	SCZ, CD, MDD, AD-response	Brief-pulse ECT	ΔHDRS pre- vs post-ECT	SCZ-PGS PT 0.05 b 0.54 SE 0.11 p < 0.0001; R^2 6.94 %; predicts greater symptom drop = & remission
Sigström et al., 2022	Swedish ECT N = 2320 (CGI-I); MADRS-S subset = 1207	MDD, BD, SCZ	ECT	CGI-I; MADRS-S response & remission	MDD-PGS OR = 0.89 p = 0.002; BD-PGS OR = 1.14 p = 0.003 (CGI-I); similar for MADRS-S outcomes
Wannemüller et al., 2021	Phobia n = 342 (dental 189; mixed 153)	EA, GAD, NEU, etc.	Exposure-based CBT	Remission & % fear reduction (post & follow-up)	Dental cohort: EA-PGS F 13.23 p = 0.0004 η^2 0.07; predicts better remission & ≥ 10 % variance in low-education subgroup
Xiong et al., 2023	Swedish MDD = 4187 (TRD definitions)	Lithium-response, AD-response	ECT proxy for TRD	Broad & narrow TRD phenotypes	Lithium-PGS OR = 1.12 p = 0.003 (FDR ≤ 0.018); explains 0.18–0.20 % liability
Xiong et al., 2025	2062 TRD cases (MDD treated with ECT after ≥1 AD trial >6 weeks) vs 441037 healthy controls; 2062 TRD vs 38544 non-TRD MDD; (Sweden subset: 1487 TRD, 1483 non-TRD, 5417 HC)	MDD, BD, SCZ, intelligence, EA, AN, NEU	ECT following ≥1 adequate AD trial (>6 weeks); ≤2 AD trials without ECT for non-TRD	TRD risk (TRD vs HC; genome-wide PRS association) and treatment resistance in MDD (TRD vs non-TRD; PRS association)	MDD-PGS: OR = 1.53 (95 % CI 1.46–1.61; FDR < 0.05); BD-PGS: OR = 1.47 (95 % CI 1.40–1.55; FDR < 0.05); SCZ PGS: OR = 1.35 (95 % CI 1.29–1.42; FDR < 0.05) for TRD risk. For treatment resistance: BD-PGS OR 1.26 (95 % CI 1.19–1.33), MDD-PGS OR 1.11 (95 % CI 1.05–1.17), intelligence PGS OR 0.94 (95 % CI 0.88–0.99); all FDR < 0.05

Legend of acronyms
AD = antidepressant; ADHD = attention-deficit/hyperactivity disorder; AN = anorexia nervosa; ANX = anxiety disorders; ARI = aripiprazole; AUG = augmentation; BD = bipolar disorder; BMI = body-mass index; CAD = coronary artery disease; CGI-I = Clinical Global Impressions–Improvement; CSF = cerebrospinal fluid; CV = cardiovascular; EA = educational attainment; ECT = electroconvulsive therapy; EHR = electronic-health-record; ESC = escitalopram; FDR = false-discovery rate; GENDEP/GENPOD/GODS/PGRN = pharmacogenetic trials; HAM-A = Hamilton Anxiety Scale; HAMD/HAM-D = Hamilton Depression Rating Scale; HC = healthy controls; HR = hazard ratio; FPG = fasting plasma glucose; HRSD = Hamilton Rating Scale for Depression; ICBT = internet-delivered cognitive behavioural therapy; IQ = intelligence quotient; HOMA-IR = homeostatic-model assessment of insulin resistance; IR = insulin resistance; MADRS = Montgomery–Åsberg Depression Rating Scale; MARS/STAR*D/UKB = cohort names; MDD = major depressive disorder; NRI = noradrenaline reuptake inhibitor; OR = odds ratio; PC = principal component; PGS = polygenic score; PT = p-value threshold of the base GWAS for SNP inclusion in the PGS; PTSD = post-traumatic-stress disorder; QIDS-C16 = Quick Inventory of Depressive Symptomatology – Clinician; RRR = relative-risk ratio; R^2 = coefficient of determination; SCZ = schizophrenia; SD = standard deviation; SNRI = serotonin-noradrenaline reuptake inhibitor; SSRI = selective-serotonin reuptake inhibitor; TEM = treatment-emergent mania; TG = triglycerides; TRD = treatment-resistant depression; TRDp = TRD proxy; trMDD = treatment-responsive MDD; WMH = white-matter hyperintensity.

negative work, most notably (Tansey et al., 2014), tested BD-PGS against SSRI outcome and reported no association; however, this outlines again the need of large samples for creating PGSs with adequate power.

3.4. ADHD PGS

Evidence for an ADHD genetic signal has been reported repeatedly. In >16,000 UK primary care patients treated with at least one antidepressant, ADHD-PGS, but not MDD-, BD- or SCZ-PGS, was associated with TRD vs non-TRD (OR = 1.09) after Bonferroni correction (Fabbri et al., 2021). A following UKB analysis replicated this finding across two proxy TRD phenotypes (ORs ~ 1.08–1.10) (Wang et al., 2025). These convergent findings are in line with clinical observations that subclinical attentional pathology may undermine antidepressant adherence and treatment outcome. However, these results were not clearly replicated in different populations with depression. In the Danish early-onset depression cohort (ages 10–25), higher ADHD-PGS reduced the probability of prolonged secondary-care contact, likely because many high-PGS individuals diverted into substance use or neurodevelopmental services (Mundy et al., 2024). In late-life depression, ADHD-PGS nominally predicted poorer improvement to venlafaxine, but p values did not survive correction (Elsheikh et al., 2024). Finally, a large GWAS using a machine-learning prediction of ECT as a proxy of TRD found a negative genetic correlation with ADHD, as well as a positive genetic correlation with EA and intelligence (Kang et al., 2024). These findings are in an opposite direction compared to most studies previously discussed, as they probably reflect a different group of patients with TRD, namely those more likely to receive ECT in the considered US clinical settings, where ECT is an expensive treatment option (Fabbri, 2025).

Thus, ADHD genetic liability seems to be consistently associated with antidepressant resistance in mid-life adults, particularly in primary care, with possible modifiers linked to age range and clinical setting.

3.5. Cardiovascular and inflammatory PGSs

The genetics of cardiometabolic and inflammatory traits contributes an additional dimension to the prediction of antidepressant outcomes. In 2019, the first SSRI trial (N = 1394) showed that CAD PGS accounted for

1.3 % of early response variance (Amare et al., 2019); responders were under-represented in the top PGS quartile (OR = 0.53). In older people, PGSs of cardiovascular traits may be particularly relevant. With this perspective, a GWAS identified the cardioembolic stroke PGS as the only Bonferroni-significant predictor of remission to venlafaxine (OR = 0.63) (Marshe et al., 2021). Neuroimaging evidence suggested possible causal mechanisms: six cardiovascular PGSs increased white matter hyperintensity (WMH) burden and, via WMH, doubled the odds of TRD (Paolini et al., 2025). In line with the inflammatory mechanisms involved in cardiovascular disease, another study reported a drug × PGS interaction, involving C reactive protein (CRP) PGS: higher CRP-PGS improved escitalopram efficacy but reduced nortriptyline one (Zwicker et al., 2018). This different effect depending on the drug is not of straightforward interpretation, as it was opposite when analysing measured serum CRP (Uher et al., 2014); therefore, state-related factors independent from genetics can be hypothesised. Finally, another study further dissected this effect by showing that CRP- and TNFα-PGSs linked specifically to appetite change and fatigue, not overall depression severity (Kappelmann et al., 2021).

In conclusion, these cardiovascular and inflammation-based PGS analyses illustrate how modest polygenic signals can contribute to elucidate treatment outcome mechanisms.

3.6. Personality and cognitive traits PGSs

PGSs for personality and cognition may modulate outcomes and provide an orthogonal behavioural perspective (Balestri et al., 2019). A two-cohort SSRI study (PGRN-AMPS/ISPC) showed that an openness PGS derived from Big-Five predicted both early non-remission and, intriguingly, superior eight-week outcomes (Amare et al., 2018), suggesting that personality traits may modulate in a complex way treatment outcome. Neuroticism-PGS had smaller but consistent negative effects in three SSRI cohorts (Ward et al., 2018) and in a further study (Amare et al., 2018), confirming the well-known clinical detrimental effect posed by high negative affectivity. Cognitive traits genetics show replicated associations with treatment outcomes. Positive associations of EA PGS with treatment outcomes were reported in samples with anxiety disorders and/or depression treated with psychotherapy (Bäckman et al., 2025; Wannemüller et al., 2021), as well as in large studies on biobank data using proxies of TRD (Xiong et al., 2025; Xu et al., 2025).

Together these studies support the evidence that PGSs for personality and cognitive traits may be relevant in the modulation of treatment outcomes, including psychotherapy response as this demands sustained self-directed learning.

3.7. Antidepressant response PGS

Even if not largely investigated as a consequence of the relatively low power compared to other traits, antidepressant response PGSs have been investigated for predicting antidepressant outcomes in independent MDD samples. The first study to provide data used for this type of analysis was a GWAS published in 2022 (N ~ 5200) (Pain et al., 2022), which provided summary statistics for remission and symptom improvement. Despite the relatively small discovery size, leave-one-out prediction reached $p < 0.05$ in five of ten cohorts; external replication was achieved in three prospective trials, Janssen (N = 190), Douglas Biomarker (N = 127) and the late-life IRL-GREY study (N = 307), with remission PGS explaining up to 0.8 % of variance. Following studies have continued to analyse these scores with encouraging findings. Remission-PGS almost doubled the odds of remission in psychotic depression treated with sertraline + olanzapine (OR = 1.95) (Men et al., 2023), and a positive association was also reported between improvement-PGS and anxiolytic effects of vortioxetine (β = 0.58) (Nøhr et al., 2022). More recently, the same score was investigated in UKB it was observed a significant link with SSRI switching (OR = 1.07) (Lo et al., 2025), whereas another recent study, which used an early-improvement outcome on escitalopram, found no association, likely due to power issues (Müller et al., 2024).

3.8. Other modulating factors

A number of variables may modulate genetic effects, such as age group and biological ageing. In late-life depression, cardiovascular PGSs may be more relevant for predicting treatment outcomes, becoming potentially more influential than PGSs for psychiatric traits on antidepressant response (Marshe et al., 2021). During pregnancy, genetic liability to psychiatric disorders appears to be irrelevant to medication trajectories: in >2000 Danish pregnancies (Liu et al., 2024) MDD-, SCZ- and BD-PGSs were not associated with the status of continuing or interrupting antidepressants, indicating that treatment decisions were driven by other factors. Among adolescents and young adults (Mundy et al., 2024), ADHD- and anorexia nervosa PGSs modulated multi-year service use rather than immediate drug response, reflecting diagnostic migration and risk of dropout. These age-sensitive patterns remind that a static PGS must be interpreted against the backdrop of changing neurobiology, hormonal status and real-world health-care pathways. Notably, most studies are framed around risk alleles, but PGSs are constructed from both risk-increasing and protective variants. The protective component has received little explicit discussion, yet is implicit in the models: individuals in the lowest PGS decile may be considered to carry relative protection, a feature supported by biobank analyses showing lower TRD odds and more favourable outcomes at the low end of MDD- or SCZ-PGS distributions.

In summary, several studies show that PGSs are consistent, albeit small, contributors to antidepressant outcome heterogeneity (Table 2). Their power is likely increased when the features of the discovery and target phenotype match, when treatment mechanisms align with the biological pathways tagged by the PGS, and when patient age group and comorbidity are properly considered.

4. Discussion

The present narrative synthesis confirms that common variant liability, as captured by PGSs, exerts a reproducible but quantitatively small influence on treatment outcomes in MDD (Fig. 1). Across

Table 2
Summary of PGS findings on MDD treatment outcome.

PGS	Monoaminergic ADs (SSRI/SNRI etc.)	Lithium/ECT/ Other	Net signal[a]
MDD	−− (6 trials + 2 EHR)	− (ECT ↓ remission)	−−
Schizophrenia	−− (4 cohorts)	++ (ECT & lithium)	± (context-specific)
Bipolar disorder	0/− (SSRI studies)	++ (lithium, ECT)	±
ADHD	−− (UKB, BioVU, MGB)	0/− (late-life venlafaxine)	−−
CAD/stroke	−− (ISPC, venlafaxine, UKB)	n/a	−−
CRP/IL-6	+/− (better escitalopram, worse nortriptyline)	n/a	±
Educational-attainment	0 (ADs)	++ (ICBT, exposure CBT)	++ (psychotherapy)
Openness (Big-Five)	− (poorer 4-wk SSRI response)	n/a	− (weak)
AD-response PGS	++ (replicated GWAS score)	++ (sertraline + olanzapine)	++
PTSD/others	− (single escitalopram study)	n/a	− (very limited)

[a] Legend: ++ = consistent better outcome, −− = consistent poorer outcome, ± = mixed/treatment-specific, **0** = null.

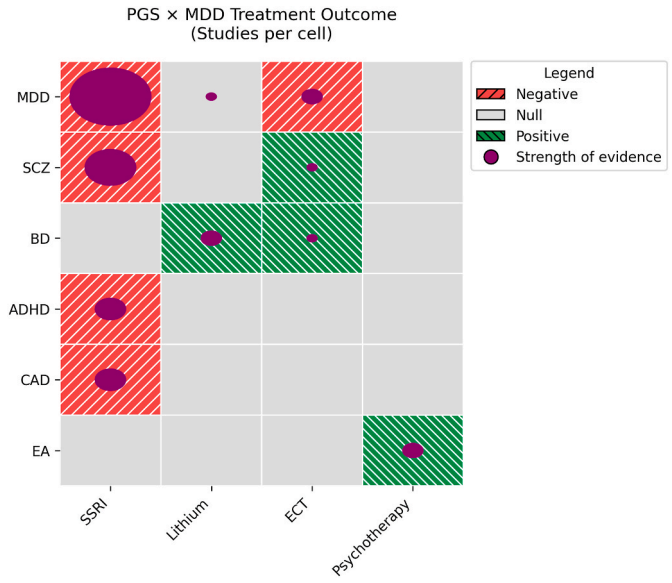

Fig. 1. The figure summarizes the effects of PGS on the different MDD treatment outcomes. The majority of studies evidence a negative correlation with SSRIs treatment outcome, mixed and less consistent findings are reported for the other treatments.

pharmacological, neuromodulatory and psychosocial interventions, effect sizes rarely exceed an OR of ~1.15 per SD increment and typically explain <1 % of outcome variance. Nevertheless, concordant associations detected in independent clinical trials and biobanks as well as for distinct treatments, strongly support that these signals are genuine rather than chance findings (Fanelli et al., 2022; Sealock et al., 2024).

Several consistent patterns of association were identified. MDD-PGS most uniformly predicts poorer SSRI/SNRI response and reduced ECT benefit, with OR~1.14 for non-remission across six European trials and OR~1.11 in large biobanks (Fanelli et al., 2022; Sealock et al., 2024; Kamp et al., 2025) including a very recent large biobank report (Lapinska et al., 2025). SCZ-PGS is similarly detrimental when considering monotherapy with monoaminergic drugs, doubling non-response risk in resistant-depression cohorts (Fanelli et al., 2021; Serretti and Baune, 2025), yet it may improve outcome to ECT or to augmentation treatments (Sigström et al., 2022), though not unequivocally (Xiong et al., 2025). BD-PGS is largely neutral when considering first-line SSRI trials, but it may predict greater response to lithium augmentation and ECT (Sigström et al., 2022; Kraft et al., 2025), whereas ADHD-PGS was associated with treatment-resistant depression (Fabbri et al., 2021). Cardiovascular and inflammatory PGSs, together with cognition-related PGS, were the most studied PGSs when considering non-psychiatric traits. A coronary artery disease PGS negatively correlates with early SSRI response (Amare et al., 2019) and, together with six cardiovascular PGSs, increases WMH burden, doubling TRD odds (Paolini et al., 2025). Behavioural-cognitive PGSs were also relevant, in particular, EA and neuroticism PGSs. Finally, PGSs derived from a GWAS of antidepressant outcomes predicted up to 0.8 % of variance in independent cohorts, and nearly double remission odds in psychotic depression treated with sertraline + olanzapine (Pain et al., 2022; Men et al., 2023).

Results convergence across multiple PGSs suggests that antidepressant outcomes are not modulated by one neurotransmitter system but instead reflect the interplay of several partially independent biological liabilities that map onto separable, yet interactive, brain circuits and peripheral pathways. In line with this hypothesis, large-scale GWASs of MDD and other major psychiatric disorders have identified specific molecular pathways and neural circuits involved in disease pathogenesis, which also show a link with the patterns of PGSs-treatment response associations summarised in our review. This convergence further supports the view that MDD, as defined by syndromic criteria, encompasses multiple biologically distinct subtypes (Nguyen et al., 2022). Grouping patients under a single diagnostic umbrella likely obscures meaningful genotype–phenotype relationships and dilutes PGS predictive power. Future efforts should prioritise biologically informed subtyping, potentially integrating dimensional constructs such as anhedonia, psychomotor slowing, executive dysfunction, or systemic inflammation. Harmonising diagnostic definitions and anchoring them to mechanistic domains may improve both predictive accuracy and therapeutic specificity. Equally important is pharmacological granularity: most existing studies grouped heterogeneous antidepressants under broad categories, a combination that may dilute PGS–outcome associations. Differentiating treatments by primary mode of action, monoaminergic, noradrenergic, multimodal, glutamatergic, would align more closely with biological subtypes such as anhedonia, cognitive dysfunction, or inflammatory–metabolic depression. Mechanism-specific analyses could reveal that certain liabilities (e.g. high SCZ-PGS) undermine serotonergic but not glutamatergic efficacy, or that cardiometabolic PGSs primarily blunt noradrenergic benefit. Future designs should therefore stratify by pharmacological class and match biological liabilities to targeted interventions.

The most recent GWAS meta-analysis of 688,808 MDD cases and 4.36 million controls identified 697 loci and 308 high-confidence genes associated with MDD, with strong enrichment for postsynaptic density scaffolds, receptor clustering proteins and other regulators of activity-dependent cytoskeletal remodelling, while serotonergic synthesis or transport genes are not over-represented (Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2025). Single-cell enrichment implicates broad classes of excitatory and inhibitory cortical neurons, medium spiny neurons and amygdala projection neurons, pointing to dysregulated synaptic plasticity across cortico-striatal-limbic loops rather than a single neurotransmitter deficit. Given that the latest trans-ancestry study reports that polygenic scores explain up to ~5.8 % of liability variance for MDD in Europeans, an upper bound for variance explained in treatment outcome can be approximated by scaling this by the squared genetic correlation between MDD liability and the outcome of interest. Empirically, the sign is adverse (higher MDD-PGS predicts poorer outcome), and published estimates suggest modest cross-trait correlations. If one assumes a genetic correlation in the 0.25–0.45 range for MDD liability versus antidepressant non-remission or TRD proxies, the expected variance explained in the outcome would be on the order of 0.4–1.2 %. This ceiling is consistent with the best-powered prospective cohorts, where MDD-PGS typically explains <1 % of outcome variance. Any real-world performance will be further attenuated by phenotype heterogeneity, drug-mix effects, ancestry mismatch and imperfect calibration. However these findings are convergent with brain imaging studies linking high MDD-PGS to blunted ventral-striatal reward and increased amygdala reactivity (Chen et al., 2025; Park et al., 2021). In this context, it is important to note that genetic liability is bidirectional: protective alleles may confer resilience to poor outcome, for example through enhanced synaptic plasticity or endothelial integrity, although such protective mechanisms have rarely been interrogated directly in antidepressant studies. A core conceptual caveat is that genetic architecture for disease risk does not necessarily map onto the molecular determinants of treatment response. Polygenic scores index variants influencing liability to develop depression, often via neurodevelopmental or pleiotropic mechanisms, whereas antidepressant efficacy reflects the capacity of adult neural circuits to adapt under pharmacological challenge. For example, SSRIs target monoaminergic transporters that are not over-represented among MDD risk loci. Similarly, many risk-associated genes exert their effects during development, long before the time window of treatment. This etiological–therapeutic gap explains why PGSs, though reproducibly associated with outcomes, explain only a fraction of variance. Nonetheless, partial overlap is plausible: polygenic burden for synaptic proteins, calcium channels, or neurotrophin

signaling could influence both susceptibility and recovery potential. However the results may also point to a mechanism explaining poor SSRIs response in cases with high MDD PGS: genetic predisposition to MDD is highly linked to alterations in glutamatergic synaptic plasticity, HPA-axis responsivity and microglial cytokine signalling, domains poorly targeted by monoaminergic drugs such as SSRIs, while treatments with different mechanisms of action may be more effective (Serretti, 2024a; Scala et al., 2023).

The GWAS of schizophrenia used to estimate SCZ-PGS in most of the cited studies included 76,755 cases and identified 287 risk loci and 120 fine-mapped genes, pointing to genes governing synaptic differentiation, vesicle cycling (*GRIN2A*, *SP4*) and the classical complement cascade (*C4A*) (Trubetskoy et al., 2022). Cell-type analyses implicated excitatory pyramidal neurons, parvalbumin interneurons, and medium spiny neurons, supporting the synaptic hypothesis of excessive microglial pruning that disrupts circuit balance and may disinhibit mesostriatal pathways, secondarily amplifying dopaminergic tone (Sellgren et al., 2019; Ferguson and Gao, 2018; Gerfen and Surmeier, 2011; Li et al., 2023). Therefore, SCZ-PGS likely captures deficits in synapse organisation and pruning. This hypothesis can explain the findings that we described: serotonergic drugs may underperform in individuals with high SCZ-PGS, whereas neuromodulation (ECT) or augmentations such as lithium may restore synaptic balance and improve outcomes, by boosting neurotrophin signalling, inhibiting GSK-3β and promoting dendritic spine recovery.

The GWAS of BD used to estimate BD PGS in most of the cited studies involved 41,917 cases and 371,549 controls; this study identified 64 loci and demonstrated that risk alleles are strongly enriched in synaptic-signalling pathways and in genes that are highly and specifically expressed in excitatory and inhibitory neurons of the prefrontal cortex and hippocampus (Mullins et al., 2021). Calcium-channel biology was highly involved: loci in *CACNA1C*, *CACNB2*, *KCNB1* and *GRIN2A* showed a significant enrichment of GWAS signal. A transcriptome-wide association study on these data implicated 15 druggable genes, most notably the serotonergic receptor *HTR6*, the melanin-concentrating-hormone receptor *MCHR1*, the neurodevelopmental protease *FURIN* and the dendrite-localised kinase *DCLK3*, whose expression changes appear causally related to BD liability. Taken together, these data suggest that BD-PGS may reflect activity-dependent synaptic plasticity and ion-channel excitability. Risk alleles converge on postsynaptic scaffolds and voltage-gated channel complexes that regulate the gain of cortico-hippocampal circuits; over-activation of these channels may lead to strain and destabilise excitation–inhibition synchrony, thereby lowering the threshold for mood switching. Lithium's clinical efficacy in high BD-PGS individuals (Song et al., 2024) is coherent with this mechanism: the drug inhibits $Ca_V1.2$ conductance and GSK-3β, amplifies neurotrophin release and re-balances synaptic signalling cascades, while ECT delivers a global neurotrophin surge that similarly restores circuit homeostasis. The enrichment in targets of calcium-channel–blockers and antiepileptic drugs among BD loci provides pharmacological corroboration and suggests these drug classes for repurposing trials in treatment-resistant depression cases with elevated BD-PGS. By reframing BD-PGS as a composite marker of synaptic-signalling load, spanning calcium influx, vesicle cycling and dendritic-spine modulation, rather than a narrow circadian or mitochondrial signature, these GWAS findings are in line with the improved lithium and ECT responses observed in this review and refine the biological axis along which bipolar liability may interact with antidepressant interventions.

The GWAS of ADHD published in 2019 (Demontis et al., 2019) identified 12 genome-wide loci, with common-variant risk highly concentrated in evolutionarily conserved sequence and in central-nervous-system regulatory elements (enrichment ~ 2.4), underscoring the neurodevelopmental aetiology of the disease. Risk alleles clustered in synaptic-signalling genes and loss-of-function-intolerant transcripts, confirming that ADHD-PGS loads broadly on neuronal integrity rather than on a single transmitter system. Functional pointed to genes central to synapse formation (*FOXP2*), dendritic vesicle trafficking (*SORCS3*), dopamine homeostasis (*DUSP6*), axon guidance (*SEMA6D*), and vesicle priming (*CADPS2*). Although gene-set enrichment did not survive multiple-testing correction, the most associated Gene-Ontology terms were "dopamine receptor binding" and "excitatory synapse", consistent with a liability axis centred on fronto-striatal neurotransmission and synaptic plasticity. These are the same circuits that support executive control, reward prediction and action selection, functions repeatedly shown to be under-active or hypo-connected in diffusion- and task-fMRI studies of adults with high ADHD burden (Tolonen et al., 2023; de Zeeuw et al., 2012; Vaidya and Stollstorff, 2008). The convergence of genetic and imaging evidence reinforces a model in which ADHD-PGS indexes reduced synaptic gain and inefficient catecholaminergic throughput along dorsolateral prefrontal–dorsal striatal loops; such inefficiency plausibly undermines behavioural activation, adherence and the sustained engagement required for antidepressant benefit. The findings of this review are in line with this hypothesis, as ADHD-PGS predicted TRD with ORs of 1.06–1.10. The genetic–clinical bridge is coherent: polygenic disruption of FOXP2- and SORCS3-mediated synaptic wiring, together with DUSP6-linked dopamine dysregulation, may yield an executive-function bottleneck that blunts both pharmacological and behavioural components of antidepressant response. Conversely, the same liability may be partially circumvented by interventions that augment dopaminergic tone (e.g., bupropion, psychostimulants), or by structured psychotherapies that externalise executive scaffolding. Finally, the broad pleiotropy of ADHD-PGS, showing positive genetic correlations with obesity, smoking and insomnia, and negative correlations with educational attainment, highlights lifestyle and health-behaviour pathways through which the score may further modulate antidepressant efficacy and cardiovascular health, leading to treatment inefficacy in mid-life depression (Du Rietz et al., 2018; Santangelo et al., 2023). Together, these findings refine our systems model: ADHD-PGS captures a composite liability spanning dopaminergic vesicle cycling, cortical–striatal synaptic density and executive network efficiency, and this liability consistently manifests clinically as antidepressant resistance unless treatments are tailored to bolster or bypass the affected circuits.

Finally, cardiometabolic PGSs add a further level of information to antidepressant pharmacogenomics. The biological pathway linking these findings could point to endothelial dysfunction. CAD and stroke risk alleles are enriched in genes governing nitric oxide synthesis (*NOS3*), vascular inflammation (*IL6R/JAK-STAT* loci), and endothelial function, promoting micro- and macro-angiopathic changes years before clinical events. Tight-junction genes (e.g., *CLDN5*) show mechanistic links to endothelial integrity (Mishra et al., 2022; Aragam et al., 2022). Cerebral small-vessel disease reduces perfusion of fronto-limbic circuits, impairs neurovascular coupling and fosters WMHs, lesions repeatedly shown to blunt SSRI efficacy in geriatric cohorts and to slow response across the age-span (Breit et al., 2023). Vascular issues also compromises drug delivery by lowering regional blood flow and, when accompanied by blood brain barrier (BBB) leakiness, permits peripheral cytokines to diffuse into the parenchyma, activating microglia and shifting tryptophan metabolism toward quinolinic-acid neurotoxicity (Marlevi and Edelman, 2021; da Fonseca et al., 2014; Lugo-Huitrón et al., 2013; Mithaiwala et al., 2021). Concomitant genetic liability to increased inflammation can exert additional detrimental effects or derive from shared genetic loci implicated also in susceptibility to cardiovascular disease. In GENDEP, a higher CRP-PGS improved escitalopram outcome but worsened nortriptyline response, revealing a significant drug × PGS interaction (Zwicker et al., 2018). CRP signals map to the *IL-6R* and *CRP* loci, both upstream of hepatic acute-phase protein synthesis; genetically driven high-CRP states therefore index a tonic, low-grade inflammation that modulates monoaminergic and noradrenergic systems differentially, potentially via cytokine-induced indoleamine-2,3-dioxygenase activation and sympathetic arousal (Ligthart et al., 2018; Interleukin-6

Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium et al., 2012; Said et al., 2022). Integration of these pathways may suggest a two-stage vascular–inflammatory gate on antidepressant efficacy. First, polygenic atherothrombotic risk gradually remodels the cerebral microvasculature, producing WMHs and hampering drug penetration into limbic targets; second, genetically elevated peripheral cytokines pass through a compromised BBB, reinforcing neuroinflammation and diminishing synaptic plasticity required for mood recovery. This model is in agreement with clinical observations that SSRIs lose efficacy in cases of high cardiometabolic burden, whereas interventions that improve endothelial health (exercise, GLP-1 receptor agonists, SGLT2 inhibitors) or dampen central inflammation (ketamine, minocycline, omega-3 fatty acids) appear beneficial in vascular-depression phenotypes (Jha et al., 2019; Ricco et al., 2017; Mone et al., 2022; Serretti, 2024b, 2024c; Chen et al., 2024; Mac Giollabhui et al., 2023).

From a translational standpoint, cardiometabolic PGSs could help to identify patients who might benefit from early cardiovascular work-up, risk-factor modification or anti-inflammatory augmentation alongside standard antidepressants. They also underscore the importance of routinely assessing WMHs and peripheral inflammatory markers in late-life and TRD cohorts, as these biomarkers reflect both genetic and environmental risk factors, and they may be more readily actionable in the clinic.

Despite modest individual effect sizes, several near-term clinical applications appear feasible. Joint MDD- and BD-PGSs could help identify patients who might benefit from early lithium augmentation or neuromodulation, shortening ineffective SSRI trials. Composite prognostic algorithms that integrate PGSs with pharmacokinetic variants (e.g., *CYP2C19/CYP2D6*), inflammatory biomarkers and clinical risk factors already explain 8–12 % of variance in pilot models (Sharew et al., 2024). Cross-trait signals highlight vascular and cognitive pathways that could be targeted by adjunctive treatments such as GLP-1 receptor agonists or cognitive-enhancement strategies, and health-economic modelling suggests that even a 5 % gain in first-line remission attributable to genotype-guided prescribing would be cost-saving if genotyping costs remain $< €50$ per patient (Lewis and Vassos, 2022). In practical terms, the question is whether any of this improves care for the average primary-care patient who receives a brief consultation and a generic SSRI. At present, routine pre-prescription PGS testing in publicly funded systems is premature: effect sizes are small, ancestry portability is limited, and the incremental value over simple clinical stratifiers at first line is uncertain. More realistic near-term pathways are: (i) research-use and service development, where PGSs enrich trials or quality-improvement pilots; (ii) targeted second-line testing after an inadequate SSRI/SNRI trial, ideally bundled with already-actionable pharmacokinetic genotypes (CYP2C19/CYP2D6) and low-cost inflammatory/cardiometabolic markers; and (iii) opportunistic use of existing genotypes (e.g., prior array data) when available in integrated records.

However several methodological caveats temper enthusiasm. Outcome definitions (e.g., response, remission, resistance, prescription proxies) vary widely across studies, hampering meta-analysis and pointing to the importance of harmonisation frameworks (Xiong et al., 2025). The ancestry bias of current GWASs, >85 % European, limits portability of PGSs to other populations and risks widening health-equity gaps. Publication bias and the "winner's curse" remain concerns, as early positive findings often attenuate in preregistered analyses. Additionally, failure to adjust for pharmacokinetic genotypes can confound associations between PGSs and treatment exposure, especially for drugs with narrow therapeutic windows (Hiemke et al., 2018; Colombo et al., 2024).

Future progress will depend on multi-ancestry discovery efforts, longitudinal cohorts with harmonised phenotyping, and integration of common-variant PGSs with rare-variant, copy number variations and epigenomic data, as illustrated by the first genome-wide-significant locus for ECT-defined TRD in SPATA16 (Xiong et al., 2025). Moreover the field is progressing, and incrementally larger and more informative GWASs, and consequent PGSs, are reported (Koromina et al., 2025; Koch et al., 2024). Pragmatic randomised trials that compare genotype-informed prescribing with treatment-as-usual are essential to demonstrate real-world benefit, while ethical research must address data privacy, counselling and reimbursement to ensure equitable implementation (Baune et al., 2023, 2024; Minelli et al., 2021). In parallel, there is growing interest in developing biologically informed PGSs (Hari Dass et al., 2019; Navarri et al., 2023; Pain et al., 2021). Unlike conventional models based purely on GWAS summary statistics, these scores incorporate functional annotations to prioritise variants likely to affect biologically relevant pathways. For antidepressant response, this could involve upweighting variants expressed in cortico-limbic neurons, microglia, or cerebrovascular endothelium, thereby improving both predictive validity and mechanistic interpretability. Moreover, integrating PGSs with dynamic -omics layers, such as transcriptomics, proteomics, or methylation, may help capture state-dependent processes that bridge static genetic liability and fluctuating treatment phenotypes. An additional, and often underappreciated, complexity is gene regulation. Transcriptional control, epigenetic modifications, and chromatin accessibility can profoundly reshape how risk alleles are expressed across development, brain regions and environmental contexts. These dynamic layers are only partially captured by static PGSs, yet they are likely to play an equally important role in determining treatment responsiveness and resilience. These multimodal approaches can identify intermediate molecular traits (e.g., cytokine profiles, neurotrophin levels) that mediate treatment response and may represent actionable targets for stratified interventions. Sex-specific effects remain largely undercharacterised. While depression prevalence and antidepressant response rates differ by sex (LeGates et al., 2019), few studies have examined whether PGS associations with outcomes are moderated by biological sex. This is particularly relevant for inflammation- and metabolism-related PGSs, where sex hormones influence immune tone, pharmacokinetics, and endothelial function (Hoffmann et al., 2023; Damoiseaux et al., 2014), potentially modifying genetic effects. Stratified analyses may reveal latent heterogeneity and improve calibration of predictive models in both research and clinical settings.

In conclusion, PGSs have progressed from statistical tools to biologically informative, partially replicable predictors of antidepressant outcomes. Although single PGSs are not yet accurate enough for clinical decisions, combinatorial models that combine various PGSs, embrace cross-trait pleiotropy and incorporate clinical covariates are steadily closing the translational gap. Meanwhile, PGSs can already provide biological insights, linking dopaminergic salience, cardiovascular health, inflammatory tone and cognitive engagement to outcome heterogeneity, and can inform hypothesis-driven trials of stratified interventions. Achieving their full potential will require global, multimodal consortia, rigorous phenotyping standards and a commitment to equity, but the trajectory toward precision psychiatry is increasingly clear.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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