

# Genetic Correlates of Treatment-Resistant Depression

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**IMPORTANCE** Treatment-resistant depression (TRD) is a major challenge in mental health, affecting a significant number of patients and leading to considerable burdens. The etiological factors contributing to TRD are complex and not fully understood.

**OBJECTIVE** To investigate the genetic factors associated with TRD using polygenic scores (PGS) across various traits and explore their potential role in the etiology of TRD using large-scale genomic data from the All of Us (AoU) Research Program.

**DESIGN, SETTING, AND PARTICIPANTS** This study was a cohort design with observational data from participants in the AoU Research Program who have both electronic health records and genomic data. Data analysis was performed from March 27 to October 24, 2024.

**EXPOSURES** PGS for 61 unique traits from 7 domains.

**MAIN OUTCOMES AND MEASURES** Logistic regressions to test if PGS was associated with treatment-resistant depression (TRD) compared with treatment-responsive major depressive disorder (trMDD). Cox proportional hazard model was used to determine if the progressions from MDD to TRD were associated with PGS.

**RESULTS** A total of 292 663 participants (median [IQR] age, 57 (41-69) years; 175 981 female [60.1%]) from the AoU Research Program were included in this analysis. In the discovery set (124 945 participants), 11 of the selected PGS were found to have stronger associations with TRD than with trMDD, encompassing PGS from domains in education, cognition, personality, sleep, and temperament. Genetic predisposition for insomnia (odds ratio [OR], 1.11; 95% CI, 1.07-1.15) and specific neuroticism (OR, 1.11; 95% CI, 1.07-1.16) traits were associated with increased TRD risk, whereas higher education (OR, 0.88; 95% CI, 0.85-0.91) and intelligence (OR, 0.91; 95% CI, 0.88-0.94) scores were protective. The associations held across different TRD definitions (meta-analytic  $R^2 > 83\%$ ) and were consistent across 2 other independent sets within AoU (the whole-genome sequencing Diversity dataset, 104 388, and Microarray dataset, 63 330). Among 28 964 individuals followed up over time, 3854 developed TRD within a mean of 944 days (95% CI, 883-992 days). All 11 previously identified and replicated PGS were found to be modulating the conversion rate from MDD to TRD.

**CONCLUSIONS AND RELEVANCE** Results of this cohort study suggest that genetic predisposition related to neuroticism, cognitive function, and sleep patterns had a significant association with the development of TRD. These findings underscore the importance of considering psychosocial factors in managing and treating TRD. Future research should focus on integrating genetic data with clinical outcomes to enhance understanding of pathways leading to treatment resistance.

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**T**reatment-resistant depression (TRD) is operationally defined as a major depressive disorder (MDD) with poor response to 2 different antidepressants.<sup>1</sup> Compared with treatment-responsive MDD (trMDD), patients with TRD have 70% more clinical visits, are 40% more likely to be hospitalized, have greater lost productivity, and have higher rates of permanent disability.<sup>2-5</sup> Patients with TRD experience up to 30% attempted suicide, with 1 in 20 dying by suicide,<sup>6</sup> leading to 30% to 50% higher mortality than individuals with trMDD.<sup>7,8</sup>

Despite the clinical significance of TRD, the etiological factors remain elusive. TRD has been associated with higher psychiatric comorbidities, including anxiety disorders, stress disorders, substance use disorder, attention-deficit/hyperactivity disorder, psychotic features, bipolarity, insomnia, and neuroticism.<sup>4,9-12</sup> However, these may indicate a distinct neurobiological origin of TRD or reflect the consequences of persistent depressive symptoms. Medical comorbidities, including diabetes, immune disorders, cardiovascular disease, and physical pain are common among patients with TRD,<sup>13,14</sup> but it is possible that those are driven by shared inflammatory processes from prolonged depression.<sup>15-17</sup> Social factors are also implicated,<sup>13,14</sup> but they can be the consequences of debilitating depressive symptoms.

Understanding the causal mechanisms of TRD is important for developing mechanism-based treatment approaches. Genetically derived polygenic scores (PGS) as causal instruments can provide insight into etiology of diseases.<sup>18</sup> Although PGS are not deterministic, the randomization in gametes let PGS be the unbiased proxies for the shared biological processes of the given traits. However, when PGS are applied to TRD studies using UK cohorts, PGS for major depression, schizophrenia, bipolar disorder, subjective well-being, intelligence, and neuroticism have shown no significant associations with TRD status,<sup>19-23</sup> despite its higher heritability than trMDD (25% vs 19%).<sup>20</sup> Thus, these findings underscore the complexity of the genetic underpinnings of TRD and suggest the need for further research to clarify associations.

Here, we performed a series of PGS analyses with data from the All of Us (AoU) Research Program, a US nationwide cohort with electronic health records (EHRs) and whole-genome sequencing (WGS).<sup>24</sup> The patterns of the associations across different depression statuses can inform us whether TRD is an extension of MDD or has distinct biological underpinnings from trMDD. To ensure the robustness of our findings, we conducted a series of sensitivity analyses on the MDD and TRD definitions, longitudinal time-to-event analyses for TRD incidence, and replication studies using 2 independent and non-overlapping cohorts within AoU.

## Methods

### AoU Research Program

We used the version 7 data release of the AoU, including 413 457 participants.<sup>24</sup> Written informed consent was obtained from all participants by the AoU Research Program. The analytic plan as a secondary data analysis is exempt from institutional re-

### Key Points

**Question** What are the predisposing characteristics among individuals who develop treatment-resistant depression (TRD)?

**Findings** This cohort study of data from 292 663 participants in the All of Us Research Program revealed that polygenic scores for traits including neuroticism, temperament, cognitive function, and sleep patterns were significantly associated with TRD. The association patterns were consistent across different TRD definitions.

**Meaning** The findings underscore the importance of considering predisposing factors when managing and treating TRD, particularly the affective and cognitive tendencies.

view board review but monitored by the Laureate Institute for Brain Research. This study followed the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) and TRIPOD reporting guidelines.

The samples were then separated into 3 independent and mutually exclusive cohorts, based on their genetic background and genotyping platforms: (1) participants who have WGS and are genetically similar to persons of European ancestry (WGS European set), (2) participants who have WGS and are genetically diverse (WGS Diverse set), and (3) participants who did not have WGS but have been genotyped with the Illumina Infinium Global Diversity Array (Microarray set). We chose these because they were predefined without random selection, enabling external replications. Stratification according to the genetic ancestry also provides more valid PGS inference and is recommended by the best practice for PGS.<sup>25</sup> Included participants self-identified with the following races and ethnicities: Asian, Black or African American, Hispanic or Latino, Middle Eastern or North African, Native Hawaiian or Other Pacific Islander, White, missing, or other, which included participants who chose “none of these fully describe me” in the questionnaire.

### Determining Status

The characterization of trMDD, TRD, and MDD negative (ie, non-MDD) was determined by diagnostic codes and the prescriptions recorded in the EHR. The mean (SD) length of the EHR was 11.89 (8.98) years. MDD status was ascertained by having at least 1 clinical visit with defined diagnostic codes while excluding those who had been diagnosed with schizophrenia and bipolar disorders (eTable 1 in Supplement 1).

We then identified the drug trial period for everyone with MDD, defined as a continuous treatment period that began with the first prescription and ended with a gap of more than 6 months without a subsequent prescription. We standardized prescription records to focus the analysis on the occurrence and continuity of antidepressants.

TRD was determined as a participant's engagement with more than 2 distinct antidepressant drugs within a single drug trial period, defined as 1 year within the starting of a continuous treatment period.<sup>26</sup> This definition was consistent with the approach used in the UK,<sup>19-23</sup> Sweden,<sup>9</sup> and Taiwan,<sup>27</sup> allowing us to systematically assess treatment patterns and the incidence of TRD across the participant cohorts.

For sensitivity analyses, we defined alternative criteria for disease status. For trMDD, these alternative definitions related to (1) requiring at least 2 clinical visits and (2) allowing for schizophrenia/bipolar diagnoses after the onset of MDD. TRD alternative definitions related to (1) varying continuous treatment periods (3 or 6 months), (2) varying the time window of the subsequent treatments (1 or 2 years), and (3) special treatments as indicators for treatment resistance (receiving electroconvulsive therapy, esketamine, or antipsychotics). In total, there were 3 different trMDD definitions and 5 different TRD definitions, resulting in 15 possible combinations (eTable 2 in Supplement 1).

## PGS

We selected 61 PGS from the following 7 domains: (1) education and cognition (2 PGS),<sup>28</sup> (2) metabolic, somatic complaints, and inflammation traits (17 PGS),<sup>29-33</sup> (3) personality (19 PGS),<sup>26,34-36</sup> (4) psychiatric disorders (9 PGS),<sup>37-43</sup> (5) sleep patterns (2 PGS),<sup>37</sup> (6) substance use (6 PGS),<sup>37,44</sup> and (7) temperament<sup>26</sup> (6 PGS). Details of each selected PGS can be found in eTable 3 in Supplement 1. The selection is based on previous studies reporting that their corresponding observed traits were associated with TRD.<sup>13,14</sup> The grouping of the domains and their associated names were according to reports in GWAS Atlas, a public data repository for summary statistics from genome-wide association studies, managed by the Department of Complex Trait Genetics at VU University Amsterdam.<sup>37</sup>

We used PRS-CS, a continuous prior-based shrinkage method,<sup>45</sup> to generate the posterior weights given the genome-wide association study summary statistics. To avoid using AoU for calibration, we used a locally available genomic dataset, the Tulsa 1000 study (T1000), including 1000 individuals with mood/anxiety, substance use, or eating disorders, and healthy controls.<sup>46</sup> The genotyping was done with the Infinium Global Screening Array (Illumina), and imputation was performed via the Michigan Imputation Server, using the Haplotype Reference Consortium reference panel.<sup>47</sup>

To calculate the PGS in AoU, we applied the derived posterior effect to the genotype data provided by AoU. Genotypes were filtered based on a preset threshold, which required that either the population-specific allele frequency exceeded 1% or the population-specific allele count was greater than 100 in any of the ancestries. We further excluded sites if they have excess heterozygosity, overall allele frequency of 0.5% or less, multinucleic alleles, or a call rate under 99%, resulting in 10 222 713 single-nucleotide variants (SNVs). For the Microarray set, the PGS were based on all available SNVs from the array, using all of the available SNVs (1 739 268). To serve as a replicating analysis, we directly applied the posterior effect sizes to the intersecting SNV sets to generate the PGS.

## Statistical Analysis

We used logistic regression for binary disease status. Covariates included 16 genetic principal components, biological sex, and age. Significance threshold was determined at  $1 \times 10^{-5}$ , a conservative threshold considering the Bonferroni correction for 2-tail tests on 61 PGS with 3 different outcome con-

trasts and additional secondary analyses. Odds ratios (ORs) and the corresponding 95% CIs are reported. For replication, we examined if effect sizes were consistent across independent cohorts. Using random-effects meta-regression, we examined how much point estimates and their uncertainties can be explained by effect sizes obtained from primary discovery cohort, using the R package metafor (R Project for Statistical Computing).<sup>48</sup>

Sensitivity analyses were used to examine the impact of the case definitions. We performed association tests of 61 PGSs on all 15 possible combinations of trMDD vs TRD. The consistency across different TRD definitions was evaluated using meta-regressions on estimated effect sizes and checking the overlap of significant associations.

To determine whether PGS were associated with progression from MDD to TRD, we selected a subset of patients with MDDs who had more than 2 diagnostic time points on record. We applied a Cox proportional hazard model to estimate the rate of TRD given the PGS while controlling for age at MDD diagnosis, sex, and 16 genetic principal components. The proportional hazard assumptions were confirmed via both a graphic method and a Schoenfeld test. All *P* values were 2-sided, and a *P* value  $< 1 \times 10^{-5}$  was considered statistically significant. Data analysis was performed using R, version 4.2.0, from March 27 to October 24, 2024.

## Results

### PGS-Associated Risk of Developing TRD

After excluding those who had missing demographic information, EHR, or genomic data, the final sample consisted of 292 663 participants (median [IQR] age, 57 (41-69) years; 175 981 female [60.1%]; 116 682 male [39.9%]) (Table 1). Participants self-identified with the following races and ethnicities: 9245 Asian (3.2%), 58 720 Black or African American (20.1%), 49 076 Hispanic or Latino (16.8%), 1635 Middle Eastern or North African (0.6%), 285 Native Hawaiian or Other Pacific Islander (0.1%), 152 395 White (52.1%), 7486 missing (2.6%), or 13 821 other (4.7%). Participants were separated into 3 cohorts: 124 945 in the WGS European set, 104 388 in the WGS Diverse set, and 63 330 in the Microarray set. eFigure 1 in Supplement 1 summarizes the associations between each PGS and disease status. In the WGS European set, 42 of our selected 61 PGS showed significant associations with the likelihood of being trMDD vs non-MDD (eTable 4 in Supplement 1). On average, the ORs had a larger magnitude in TRD vs non-MDD than in trMDD vs non-MDD comparisons. Despite a high degree of similarity in the association patterns, 11 PGS showed stronger associations with TRD than with trMDD (eFigure 1 in Supplement 1 and Figure 1). Those 11 PGS belong to 4 different domains: education/cognition, sleep, personality, and temperament. The significant PGS in temperament represent transdiagnostic recent affect, such as lethargy, depressed mood, and tenseness in the past 2 weeks. However, none of the PGS for psychiatric disorders, including PGS for MDD, were shown to significantly differentiate TRD from trMDD.

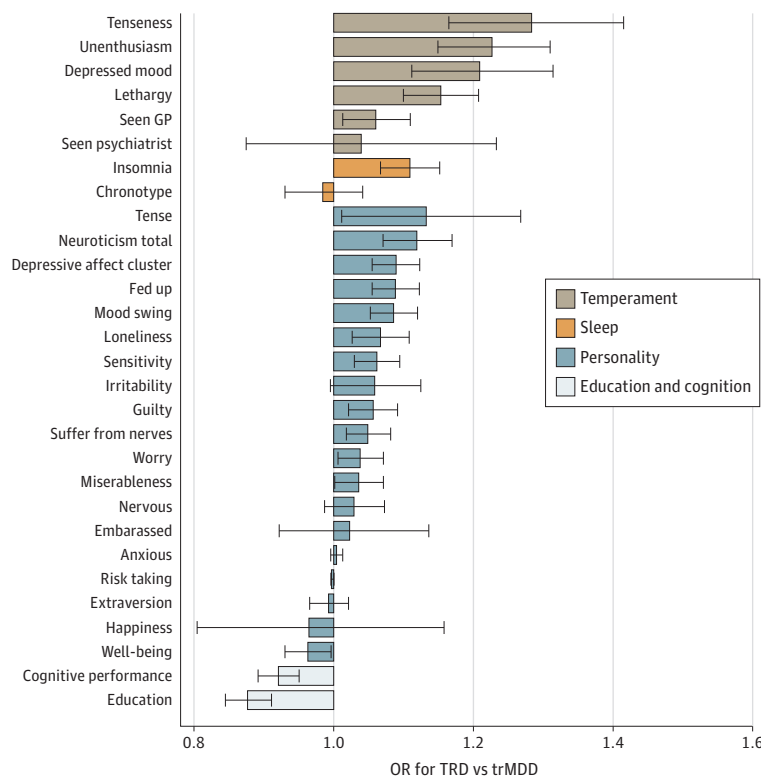
Table 1. Demographic Characteristics

Variable	WGS, European set			WGS, Diverse set			Microarray set		
	Non-MDD (n = 104 128)	trMDD (n = 16 640)	TRD (n = 4177)	Non-MDD (n = 93 881)	trMDD (n = 8578)	TRD (n = 1929)	Non-MDD (n = 55 801)	trMDD (n = 6106)	TRD (n = 1423)
Sex, No. (%)									
Female	59 921 (57.5)	11 554 (69.4)	2975 (71.2)	55 820 (59.5)	6386 (74.4)	1492 (77.3)	32 633 (58.5)	4207 (68.9)	993 (69.8)
Male	44 207 (42.5)	5086 (30.6)	1202 (28.8)	38 061 (40.5)	2192 (25.6)	437 (22.7)	23 168 (41.5)	1899 (31.1)	430 (30.2)
Birth year, median (range)	1961 (1905-2004)	1960 (1918-2003)	1962 (1926-2003)	1972 (1915-2004)	1966 (1923-2003)	1966 (1930-2002)	1966 (1901-2004)	1962 (1921-2004)	1965 (1924-2001)
Self-reported race and ethnicity, No. (%)									
Asian	27 (0)	5 (0)	0	6750 (7.2)	308 (3.6)	55 (2.9)	2029 (3.6)	60 (1.0)	11 (0.8)
Black or African American	82 (0.1)	17 (0.1)	3 (0.1)	42 249 (45.0)	3750 (43.7)	944 (48.9)	10 357 (18.6)	1036 (17.0)	282 (19.8)
Hispanic or Latino	877 (0.8)	100 (0.6)	21 (0.5)	33 791 (36.0)	3393 (39.6)	676 (35.0)	9246 (16.6)	823 (13.5)	149 (10.5)
Middle Eastern or North African	434 (0.4)	43 (0.3)	8 (0.2)	662 (0.7)	61 (0.7)	17 (0.9)	373 (0.7)	31 (0.5)	6 (0.4)
Native Hawaiian or Other Pacific Islander	19 (0)	1 (0)	0	166 (0.2)	11 (0.1)	2 (0.1)	82 (0.1)	4 (0.1)	0
White	97 366 (93.5)	15 579 (93.6)	3907 (93.5)	1248 (1.3)	126 (1.5)	32 (1.7)	29 592 (53.0)	3694 (60.5)	851 (59.8)
Missing	2551 (2.4)	504 (3.0)	143 (3.4)	2367 (2.5)	200 (2.3)	51 (2.6)	1441 (2.6)	181 (3.0)	48 (3.4)
Other <sup>a</sup>	2772 (2.7)	391 (2.3)	95 (2.3)	6648 (7.1)	729 (8.5)	152 (7.9)	2681 (4.8)	277 (4.5)	76 (5.3)

Abbreviations: MDD, major depressive disorder; TRD, treatment-resistant depression; trMDD, treatment-responsive MDD.

<sup>a</sup> Other race and ethnicity includes participants who chose "none of these fully describe me" in the questionnaire.

Figure 1. Polygenic Score (PGS) Domains Containing Significant Associations With Treatment-Resistant Depression (TRD) Status



The distribution of the odds ratios (ORs) in the domains where individual PGS show significant associations with TRD status than with treatment-responsive major depressive disorder (trMDD). The x-axis represents the ORs when compared with non-MDD groups, for every 1-SD increase in PGS. The y-axis represents each included PGS. GP indicates general practitioner.

**Table 2. Summary of the Sensitivity Analyses on the Definitions of Treatment-Resistant Depression (TRD) and Treatment-Responsive Major Depressive Disorder (trMDD)**

Comparison sets	trMDD, No.	TRD, No.	Effect size consistency (meta $R^2$ )	No. of significant PGS	Overlapping with the primary 11 PGS <sup>a</sup>
Primary result (TRD <sub>1</sub> vs trMDD <sub>1</sub> ) <sup>b</sup>	16 640	4177	100	11	100
TRD <sub>2</sub> vs trMDD <sub>1</sub>	13 866	5127	96.1	11	91
TRD <sub>3</sub> vs trMDD <sub>1</sub>	13 932	5328	95.7	8	73
TRD <sub>4</sub> vs trMDD <sub>1</sub>	16 544	4206	100	11	100
TRD <sub>5</sub> vs trMDD <sub>1</sub>	13 454	8392	90.5	17	100
TRD <sub>1</sub> vs trMDD <sub>2</sub>	13 275	3818	100	10	91
TRD <sub>2</sub> vs trMDD <sub>2</sub>	11 340	4760	96.3	12	91
TRD <sub>3</sub> vs trMDD <sub>2</sub>	11 377	4929	95.2	9	82
TRD <sub>4</sub> vs trMDD <sub>2</sub>	13 253	3870	100	10	91
TRD <sub>5</sub> vs trMDD <sub>2</sub>	10 677	7324	95.2	17	100
TRD <sub>1</sub> vs trMDD <sub>3</sub>	16 570	4145	100	11	100
TRD <sub>2</sub> vs trMDD <sub>3</sub>	14 677	5804	95.5	10	91
TRD <sub>3</sub> vs trMDD <sub>3</sub>	14 705	6052	95	9	82
TRD <sub>4</sub> vs trMDD <sub>3</sub>	16 544	4278	100	11	100
TRD <sub>5</sub> vs trMDD <sub>3</sub>	13 454	9747	84.3	21	100

Abbreviation: PGS, polygenic score.

<sup>a</sup> Significance threshold set at  $P$  values in  $1 \times 10^{-5}$ .

<sup>b</sup> The rubric for the TRD and MDD definitions is detailed in eTable 2 in Supplement 1 and can be summarized as follows: trMDD<sub>1</sub> is the definition used in the primary results; those with at least 1 clinical visit with psychiatric diagnoses specified in the inclusion criteria, excluding psychosis and bipolar disorders, have consecutive drug treatment, and are not categorized as TRD. trMDD<sub>2</sub> includes those who have at least 2 clinical visits with psychiatric diagnoses specified in the inclusion criteria, excluding psychosis and bipolar disorders, have consecutive drug treatment, and are not categorized as TRD. trMDD<sub>3</sub> includes those who have at least 1 clinical visit with psychiatric diagnoses specified in the inclusion criteria, no exclusion of psychosis and bipolar after first MDD diagnoses, have consecutive drug treatment, and are not categorized as TRD. TRD<sub>1</sub> is the definition used in the primary results; those with MDD (depending on the MDD definition specified before) who

have received consecutive drug treatment within 6 months and have subsequent medication change within 1 year. TRD<sub>2</sub> includes those with MDD (depending on the MDD definition specified before) who have received consecutive drug treatment within 3 months and have subsequent medication change within 1 year. TRD<sub>3</sub> includes those with MDD (depending on the MDD definition specified before) who have received consecutive drug treatment within 6 months and have subsequent medication change within 2 years. TRD<sub>4</sub> includes those with MDD (depending on the MDD definition specified before) who have received consecutive drug treatment within 6 months and have subsequent medication change within 1 year or receiving last-line treatment (electroconvulsive therapy or esketamine). TRD<sub>5</sub> includes those with MDD (depending on the MDD definition specified before) who have received consecutive drug treatment within 6 months and have subsequent medication change within 1 year or receiving the last-line treatment (electroconvulsive therapy or esketamine) or antipsychotics.

Genetic propensity for temperament had an increased OR for TRD (unenthusiasm: OR, 1.11; 95% CI, 1.07-1.15; lethargy: OR, 1.14; 95% CI, 1.10-1.18; tenseness: OR, 1.15; 95% CI, 1.10-1.21; depressed mood: OR, 1.10; 95% CI, 1.05-1.14). Insomnia increased TRD risk by 1.11 fold (OR, 1.11; 95% CI, 1.06-1.15). Neuroticism and its item-level subscores all increased the likelihood of being TRD (1.11; 95% CI, 1.07-1.16). PGS predicting higher educational attainment and cognitive performance were associated with lower prevalence of TRD, with an OR of 0.88 (95% CI, 0.84-0.91) and 0.91 (95% CI, 0.89-0.95), respectively, as was intelligence (OR, 0.91; 95% CI, 0.88-0.94). Considering TRD groups had a slightly higher proportion of females, we followed up with sex-stratified analyses. None of the PGS showed evidence of sex-specific or interactive effects in TRD vs trMDD (eTable 5 in Supplement 1).

### Replication on 2 Independent Sets

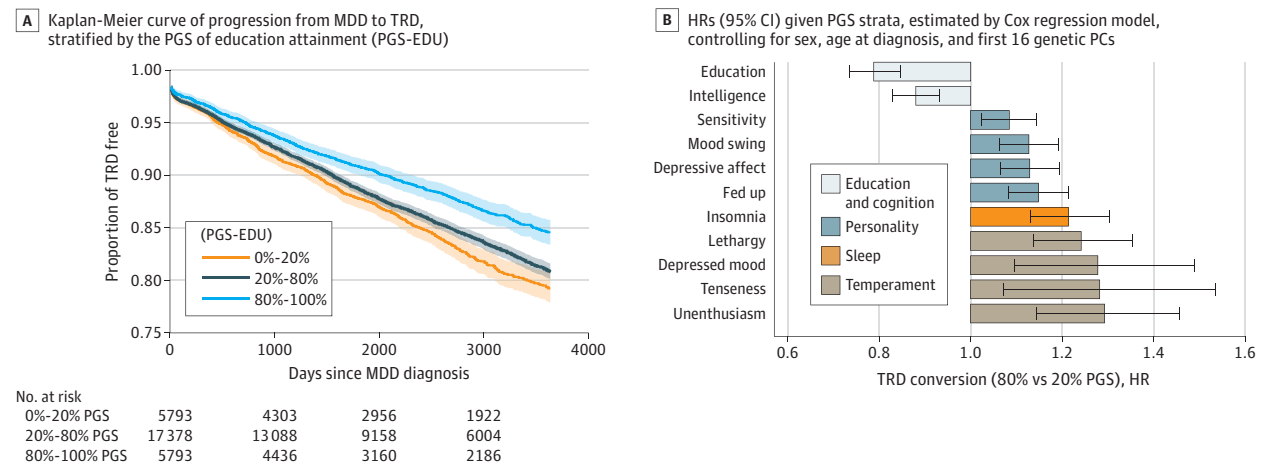
We performed the same association tests in the replication sets while examining the consistencies via random effects meta-analyses. We found that the associations were highly consistent across 2 other independent sets within AoU (the whole-genome sequencing Diverse set, 104 388, and Microarray set, 63 330). Meta-analytic  $R^2$  between the WGS Diverse set and European set were 95% and 94% for trMDD vs non-MDD and TRD

vs non-MDD comparisons, respectively (eFigures 2 and 3 in Supplement 1). Estimates on TRD vs trMDD derived independently for the European and Diversity cohorts have meta-analytic  $R^2$  at 93% (eFigure 4 in Supplement 1). These results were also replicated in the Microarray set, despite fewer SNVs and fewer individuals compared with the WGS dataset (eFigure 5 in Supplement 1). The meta-analytic  $R^2$  for TRD vs trMDD was 78% in the Microarray set. PGS of cognition, education attainment, and insomnia remained significantly associated with TRD (education:  $P = 9.5 \times 10^{-7}$ ; cognition:  $P = 1.58 \times 10^{-3}$ ; insomnia:  $P = 8.5 \times 10^{-3}$ ).

### Sensitivity Analysis of the Definition of trMDD and TRD

To investigate the impact of different definitions of trMDD and TRD, we performed sensitivity analyses on our discovery cohort, repeating the same PGS analyses with various case definitions. Across 15 possible combinations of trMDD vs TRD, the effect size distributions and the number of significant associations are highly consistent (Table 2 and eTable 6 in Supplement 1). Despite different criteria in defining trMDD and TRD, all have meta-analytic  $R^2$  above 95% compared with the primary results, except the pairs that included individuals who received antipsychotics. Six of 14 pairs have the same set of 11 PGSs shown to be significantly associated with TRD status.

**Figure 2. Progression Rates of Treatment-Resistant Depression (TRD) From the First Major Depressive Disorder (MDD) Diagnosis in the Longitudinal Cohort**



A, Kaplan-Meier curve of progression from MDD to TRD, stratified by the polygenic scores (PGS) of education attainment (PGS-EDU). Individuals were grouped by their PGS as follows: 0 to 20 percentile, 20 to 80 percentile, and

80 to 100 percentile. B, Hazard ratios (HRs) and the corresponding 95% CIs given PGS strata, estimated by Cox regression model, controlling for sex, age at diagnosis, and first 16 genetic principal components (PCs).

Among those 11 PGSS, 8 remained significant across all scenarios. Those were PGS for neuroticism and its subscales, recent affects, insomnia, education attainment, and cognitive performance. PGS for schizophrenia, smoking status, and somatic complaints became significantly associated with TRD status only among individuals who received antipsychotics (TRD<sub>5</sub> sets), suggesting a potential confound by indications. The associations held across different TRD definitions (meta-analytic  $R^2 > 83\%$ ).

### Predicting the Progression From MDD to TRD

To determine whether PGS were associated with progression from MDD to TRD, we selected a subset of patients with MDDs who had more than 2 diagnostic time points on record (19 124 in the WGS European set, 9840 in the WGS Diverse set, and 6967 in the Microarray set). Among 28 964 individuals from the WGS set who had at least 2 time points, 3854 converged to TRD, on average, within 944 days after receiving MDD diagnosis (95% CI, 883-992 days). As showcased in **Figure 2A**, when individuals were stratified by the PGS of educational attainment (PGS-EDU), higher level of PGS-EDU was associated with a slower progression rate to TRD than those who have lower level of PGS-EDU (Kaplan-Meier curves for each PGS strata and corresponding 95% CI). We formally tested the time-modulating effects of those PGS using proportional hazard models. **Figure 2B** shows the hazard ratios (HRs) estimated from the analyses of time to TRD onset in the longitudinal WGS sets. All previously identified 11 PGS showed significant associations with time to TRD onset, except 2 subitems of neuroticism. For instance, higher PGS-EDU (80 percentile) was associated with slower progression rate compared with lower PGS-EDU (20 percentile; HR, 0.79; 95% CI, 0.74-0.85). Higher PGS for insomnia (80 percentile) was associated with a faster progression rate compared with lower PGS for insomnia (20 percentile; HR, 1.21; 95% CI, 1.13-1.30). These results suggest that

genetic propensity of those traits was associated with the progression of treatment responsiveness, as the emergence of TRD. We repeated the analyses on the Microarray subset and found consistent effect sizes, as meta-analytic  $R^2$  in 100% (**eFigure 6** in **Supplement 1**).

### Discussion

Our findings showed that increased risks of TRD were genetically correlated with traits such as depressive affect, neuroticism, and insomnia. Conversely, traits related to cognition and education showed a protective association against TRD. These results were robust across different case definitions and replicated in 2 independent AoU datasets, supporting that these traits were etiological factors for TRD.<sup>13,14</sup> Our findings highlight not only the genetic predispositions associated with TRD but also demonstrate the complex interplay of traits associated with the development of TRD.

Variations in TRD definitions and the study samples can lead to a wide range of SNV heritability, reported to be between 8% and 25%.<sup>20,49</sup> Because the statistical power of PGS depends on the heritability of the trait of interest,<sup>50</sup> the association patterns of PGS can be sensitive to the definition of TRD and the sample compositions. Our identified 11 PGS were consistently associated with TRD throughout different definitions and replications, indicating their critical roles in the emergence of treatment resistance. Meanwhile, genetic propensity for psychiatric conditions did not differentiate treatment responsiveness, echoing results from similar studies conducted with UK samples.<sup>19,21,23</sup> This suggests that the higher comorbidities among patients with TRD likely reflect the consequence of prolonged depression instead of shared etiological factors across different psychiatric diagnoses. The salient predisposing factors are constitutional characteristics that are

more malleable by socioenvironmental context, such as cognitive functioning, temperament, and neuroticism, underscoring the complexity of diagnosing and treating these severe forms of depression.

Neuroticism is a highly heritable personality trait that reflects a tendency to experience negative emotions, such as anxiety, depression, anger, and fear, in response to stressors or challenges.<sup>35,36</sup> Our results highlight the significant association of neuroticism with both the onset and treatment resistance of MDD. Strong associations with TRD support that specific subtypes of neuroticism, such as the depressive affect cluster, are linked to more severe progression of MDD,<sup>19,51-58</sup> highlighting the shared genetic components between the depressive tendencies as a personality trait and the severity of the depressive symptoms as a treatment outcome.

The finding that high neuroticism was associated with greater treatment resistance may also be mediated by reduced cognitive flexibility. Neuroticism is deeply intertwined with cognitive processes that exacerbate depressive disorders,<sup>59-61</sup> rendering it resistant to conventional treatments. The potential involvement of biased cognitive processes in the etiology of TRD is further supported by our findings of the protective associations of educational attainment and cognitive performance. Such findings align with previous studies that have noted phenotypic associations between higher education levels and reduced TRD risk.<sup>11,12,62,63</sup> However, PGS for education attainment is also known to be associated with socioeconomic status,<sup>64,65</sup> underscoring the likely multifactorial contributions between education attainment and the emergence of TRD. The evidence highlights the importance of considering factors that may influence decision processes in the management of TRD, emphasizing the need for further investigation into how genetic predispositions and environmental factors impact treatment outcomes and resistance.

We found that insomnia was significantly associated with the TRD risk. Sleep disturbances are deeply intertwined with depressive symptoms and are a key feature among patients with TRD.<sup>9,66,67</sup> Although treating insomnia could alleviate depressive symptoms,<sup>67</sup> pharmacological intervention with benzodiazepine is deemed to be inadequate or even harmful to pa-

tients with TRD.<sup>66,68</sup> The association between PGS for insomnia and TRD may be driven by a shared etiology, potentially explaining why psychotropic agents, such as ketamine, can simultaneously ameliorate both the depressive symptoms and sleep disturbance among patients with TRD.<sup>69</sup>

### Limitations

Our study has limitations. TRD status was determined by an algorithm using drug events in EHR, lacking detailed symptom measures, nondrug treatments, and adherence data. Those factors might lead to misclassifications, reducing the statistical power to detect associations. However, our extensive sensitivity analyses show that the identified associations were robust across scenarios. Socioeconomic factors may still have contributed to the time to TRD onset despite our efforts to control confounds. The associations could be driven by treatment-seeking behaviors and the affordability of provided care, as PGS may be related to those mediating factors rather than underlying biological mechanisms of TRD. Additionally, PGS capture genetic predispositions rather than full environmental exposures; therefore, PGS may not fully reflect traits driven mainly by environmental factors, such as adversity<sup>13,14,70</sup> and stress.<sup>70,71</sup>

### Conclusions

In conclusion, this comprehensive cohort study has brought to light several genetic factors that may influence the development and management of TRD. Despite the complex genetic landscape of TRD, our findings across definitions of TRD and independent datasets were consistent and robust. The association between high levels of neuroticism and TRD suggests a common emotional/cognitive process that may be the target of treatment strategies. The identification of insomnia as a treatable risk factor offers a viable pathway for clinical intervention. These insights not only advance our understanding of the genetic underpinnings of TRD but also highlight potential ways to improve outcomes for those experiencing this challenging condition.

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