Polygenic risk scores for precision psychiatry: a study on the effect heterogeneity of antidepressants

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November 2, 2024

Abstract

Depression continues to be a major contributor to the global burden of diseases. Antidepressants are recommended as the initial choice of treatment for moderate and severe depression among adults, but the choice of antidepressant class can be challenging, as efficacies of commonly used antidepressants are generally comparable between classes. As such, to determine which medication to prescribe to each patient, clinicians often rely on the adverse effect profile of antidepressants. One of the most discussed adverse effects is the possibility of increased suicidality with antidepressant initiation, a rare but serious adverse event. Efforts to predict this have mostly relied on clinical and sociodemographic characteristics of patients, but we do not yet have a clear picture. A promising avenue is to use patients' genetic data, but the evidence on its utility has so far been mixed, and few large scale databases have both clinical and genetic data that can evaluate its utility. Here, using genetic and clinical data on more than 7,000 patients, both children and adults, with major depressive disorder from the All of Us Research Program, we show that the genetic predisposition for psychiatric disorders may underlie the substantial heterogeneity in the risk of suicidal thoughts with antidepressant use. Specifically, using a target trial emulation framework, we show that patients with higher polygenic risk scores for psychiatric disorders, particularly for attention deficit-hyperactivity disorder, are more likely than those with lower scores to experience suicidal thoughts with the use of selective serotonin reuptake inhibitors, relative to bupropion. In the personalized medicine framework, PRSs for various psychiatric disorders may help tailor antidepressants to each patient to avoid serious adverse effects such as suicidal thoughts.

Main

Depression is a psychiatric disorder that continues to put large burden worldwide [1]. Several evidence-based treatments exist for the disorder, including pharmacotherapy, psychotherapy, electroconvulsive therapy, and transcranial magnetic stimulation. Antidepressants are recommended as the initial choice of treatment for moderate and severe depression among adults. Because the efficacies of commonly used antidepressants are generally comparable between classes, the choice of antidepressants will largely be based on the adverse effect profile [2]. However, the challenge lies in predicting the adverse effects, which is essential in determining which patients to prescribe the most commonly-used selective serotonin reuptake inhibitors (SSRIs) or to prescribe alternative medications such as serotonin and norepinephrine reuptake inhibitors (SNRIs) or bupropion. This is a question that has come up repeatedly in clinical psychiatry, but one without a clear answer [3]. Currently, finding the appropriate medication for each patient usually requires trial-and-error, and the delayed therapeutic effects of antidepressants makes this even more challenging [4].

Among the adverse effect profiles of antidepressants, perhaps one that has received the most attention is the possibility of increased suicidality with antidepressant initiation, the so called "black-box" warning of antidepressants by the Food and Drug Administration [5, 6]. As a result, clinicians have sought to predict suicidal behavior among antidepressant users, first using patients' clinical and sociodemographic characteristics. Though several potential predictors have been found, conclusive evidence is still lacking [3, 7]. One exception may be younger age, which has been reported to be associated with increased suicidal behavior with antidepressant initiation [8], but this has sparked considerable debate, with some calls to remove the "black-box" warning amidst declining antidepressant prescription rates that led to the Food and Drug Administration's modification of the warning [5]. As such, better predictors of antidepressants' adverse events are needed to better inform practice.

Researchers have thus turned to patients' genetics, including polygenic risk scores (PRSs), to better understand factors that may help predict antidepressant response. This may be a promising avenue given the growing evidence that psychiatric disorders, including depression, are typically complex traits, with variants associated with these diseases dispersed across the allelic spectrum [9]. There have been many studies on the link between the effectiveness of antidepressants and PRSs for depression. For instance, studies have pointed to associations between a higher PRS for major depressive disorder and a prescription of more than two antidepressants [10] as well as changes in depression scores with SSRI use [11].

There have also been attempts to guide antidepressant choice with PRSs for other psychiatric disorders, namely schizophrenia, bipolar disorder, and attention-deficit hyperactivity disorder (ADHD), each of which shares genetic factors with depression [12, 13]. For instance, PRS for schizophrenia was not associated with changes in depression scores after treatment with SSRIs, though the study may have been underpowered [14]. Though some suggest that non-response to antidepressants may be due to undiagnosed bipolar disorder, bipolar disorder PRS was not associated with antidepressant response [15]. Finally, studies on PRSs for ADHD, a common comorbidity of major depressive disorder [16], was associated with higher odds of prescription of multiple antidepressants [10].

These findings, though valuable, have mostly focused on antidepressant response and less on the adverse effects of antidepressants. However, clinicians often base their choice of antidepressants on the possibility of serious adverse events such as suicidal behavior, especially when prescribing to young people [5]. As such, we aimed to provide evidence on the effects of different types of antidepressants with the goal of advancing precision/genomic medicine and guiding clinical practice. We focus on antidepressants that are primarily used in clinical practice: SSRIs, SNRIs, and bupropion [2]. Importantly, SNRIs and bupropion are viable alternatives to SSRIs, which are often considered to be first-line antidepressants; thus, this study can inform for whom these medications should be used in place of SSRIs. Equally as important, we evaluate the antidepressants' effects on suicidal ideation, which is of utmost clinical importance both as a primary outcome (as one of the main symptoms of depression) and as a potential adverse event.

Results

Target trial emulation of antidepressants

We used the target trial emulation framework [17] on All of Us Research Program data [18] to compare the effects of three types of antidepressants (SSRIs, SNRIs, and bupropion) on suicidal thoughts, across demographic and clinical characteristics as well as PRSs for psychiatric disorders. A total of 7,848 participants were matched for SSRIs vs. bupropion and 9,316 participants were matched for SSRIs vs. SNRIs, and both samples included children and adults. In the SSRIs vs. bupropion sample, 68.0% were female, the mean age was 47.8 years (standard deviation (SD), 14.4), and 11.3% identified as Hispanic and 14.4% as Non-Hispanic Black. Among the previous diagnoses surveyed, anxiety was the most prevalent at 9.4%. In the SSRIs vs. SNRIs sample, 71.1% were female, the mean age was 49.6 (standard deviation (SD), 14.3), and 12.2% identified as Hispanic and 15.1% as Non-Hispanic Black. Among the previous diagnoses surveyed, anxiety was the most prevalent at 9.0%. Both the SSRIs vs. bupropion and SSRIs vs. SNRIs samples achieved good balance of covariate distributions, including previous diagnoses of psychiatric disorders and PRSs (Tables 1 and 2).

The sources of the selected PRSs and links in the PGS catalog are available in Extended Data Table 1. In general, the PRSs achieved modest performance in predicting the psychiatric disorders (AUROCs up to 0.67), though in some cases the AUROCs were close to 0.5. They tended to perform worse in groups other than non-Hispanic Whites (Extended Data Figures 1-6).

We fit Cox proportional hazard models to estimate hazard ratios of the risks of suicidal thoughts associated with antidepresssant use. SSRIs had a higher risk of suicidal thoughts relative to bupropion (hazard ratio, 1.36; 95% confidence interval (CI), 1.14 to 1.63; P-value < 0.001; Figure 1a). In contrast, SSRIs and SNRIs had comparable risks of suicidal thoughts (hazard ratio of SSRIs relative to SNRIs, 1.05; 95%CI, 0.91 to 1.22; P-value = 0.50; Figure 1b)

Table 1: Comparison of matched bupropion and SSRI samples[a]

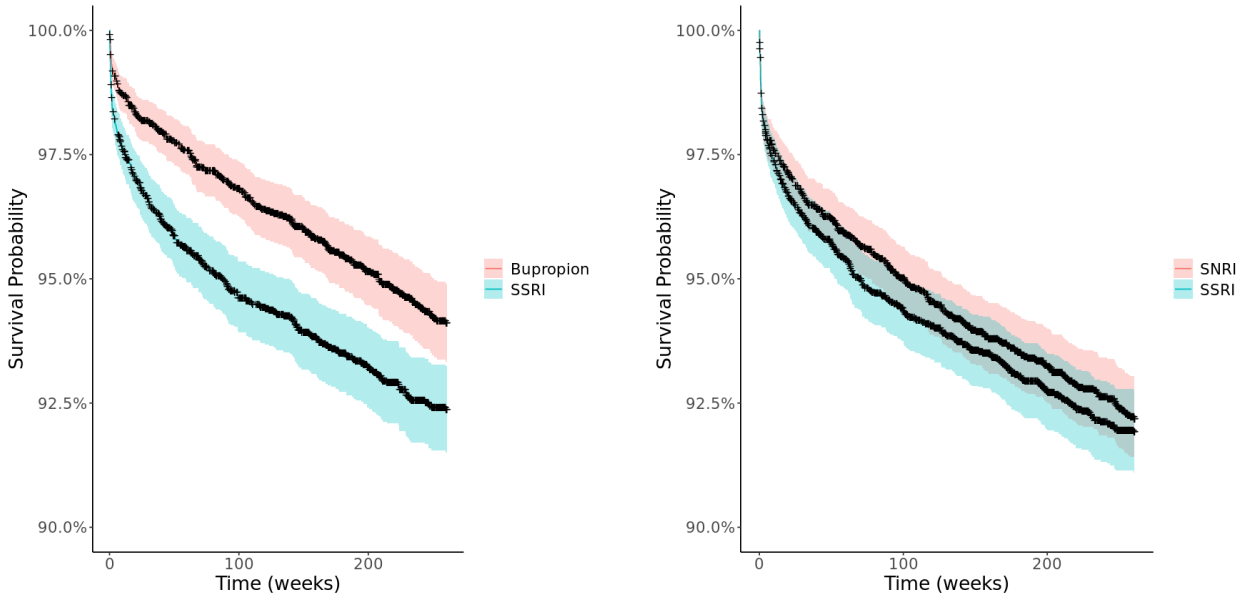
	Bupropion n = 3924	SSRI n = 3924	SMD
Gender (%)			0.048
Female	2631 (67.0)	2704 (68.9)	
Male	1267 (32.3)	1187 (30.2)	
Other	26 (0.7)	33 (0.8)	
Age (mean (SD))	47.93 (14.08)	47.58 (14.76)	0.024
Race and ethnicity (%)			0.099
Hispanic	391 (10.0)	497 (12.7)	
Non-Hispanic Black	542 (13.8)	590 (15.0)	
Non-Hispanic White	2814 (71.7)	2659 (67.8)	
Other	177 (4.5)	178 (4.5)	
College education or higher (%)	3030 (77.2)	2906 (74.1)	0.074
Annual income (%)			0.077
-$25,000	1315 (33.5)	1420 (36.2)	
$25,000-$50,000	785 (20.0)	830 (21.2)	
$50,000-$100,000	987 (25.2)	909 (23.2)	
$100,000-	837 (21.3)	765 (19.5)	
Has health insurance (%)	3823 (97.4)	3765 (95.9)	0.083
Born in the US (%)	3621 (92.3)	3555 (90.6)	0.060
Ever-smoker (%)	2180 (55.6)	1975 (50.3)	0.105
Previous diagnosis of suicidal thoughts (%)	148 (3.8)	210 (5.4)	0.076
Previous diagnosis of anxiety (%)	338 (8.6)	396 (10.1)	0.051
Previous diagnosis of alcohol abuse (%)	218 (5.6)	227 (5.8)	0.010
Previous diagnosis of substance abuse (%)	183 (4.7)	198 (5.0)	0.018
Previous diagnosis of schizophrenia (%)	54 (1.4)	52 (1.3)	0.004
Previous diagnosis of eating disorders (%)	12 (0.3)	12 (0.3)	<0.001
Previous diagnosis of PTSD (%)	244 (6.2)	254 (6.5)	0.010
Previous diagnosis of ADHD (%)	194 (4.9)	138 (3.5)	0.071
Previous tricyclic antidepressant use (%)	351 (8.9)	339 (8.6)	0.011
PRS for depression (mean (SD))	0.00 (1.03)	0.02 (0.98)	0.018
PRS for suicidal thoughts (mean (SD))	0.05 (0.99)	0.05 (1.01)	0.001
PRS for anxiety (mean (SD))	-0.01 (1.01)	-0.01 (1.01)	0.005
PRS for bipolar disorder (mean (SD))	-0.19 (0.98)	-0.16 (0.98)	0.029
PRS for schizophrenia (mean (SD))	-0.29 (0.92)	-0.23 (0.94)	0.067
PRS for ADHD (mean (SD))	-0.14 (0.96)	-0.10 (0.97)	0.037

[a] Each PRS was standardized across the full All of Us Research Program sample prior to analyses. SSRI, serotonin reuptake inhibitor; PTSD, post-traumatic stress disorder; ADHD, attention deficit-hyperactivity disorder; PRS, polygenic risk score.

Table 2: Comparison of matched SNRI and SSRI samples[b]

	SNRI n = 4658	SSRI n = 4658	SMD
Gender (%)			0.063
Female	3376 (72.5)	3248 (69.7)	
Male	1240 (26.6)	1371 (29.4)	
Other	42 (0.9)	39 (0.8)	
Age (mean (SD))	50.47 (13.80)	48.69 (14.70)	0.125
Race and ethnicity (%)			0.070
Hispanic	528 (11.3)	608 (13.1)	
Non-Hispanic Black	683 (14.7)	725 (15.6)	
Non-Hispanic White	3248 (69.7)	3104 (66.6)	
Other	199 (4.3)	221 (4.7)	
College education or higher (%)	3515 (75.5)	3404 (73.1)	0.055
Annual income (%)			0.048
-$25,000	1885 (40.5)	1877 (40.3)	
$25,000-$50,000	991 (21.3)	927 (19.9)	
$50,000-$100,000	1018 (21.9)	1019 (21.9)	
$100,000-	764 (16.4)	835 (17.9)	
Has health insurance (%)	4526 (97.2)	4490 (96.4)	0.044
Born in the US (%)	4288 (92.1)	4236 (90.9)	0.040
Ever-smoker (%)	2380 (51.1)	2286 (49.1)	0.040
Previous diagnosis of suicidal thoughts (%)	208 (4.5)	271 (5.8)	0.061
Previous diagnosis of anxiety (%)	384 (8.2)	459 (9.9)	0.056
Previous diagnosis of alcohol abuse (%)	233 (5.0)	285 (6.1)	0.049
Previous diagnosis of substance abuse (%)	189 (4.1)	236 (5.1)	0.048
Previous diagnosis of schizophrenia (%)	53 (1.1)	71 (1.5)	0.034
Previous diagnosis of eating disorders (%)	7 (0.2)	13 (0.3)	0.028
Previous diagnosis of PTSD (%)	340 (7.3)	353 (7.6)	0.011
Previous diagnosis of ADHD (%)	140 (3.0)	172 (3.7)	0.038
Previous tricyclic antidepressant use (%)	572 (12.3)	399 (8.6)	0.122
PRS for depression (mean (SD))	0.02 (1.04)	0.03 (1.00)	0.015
PRS for suicidal thoughts (mean (SD))	0.06 (1.02)	0.05 (1.01)	0.016
PRS for anxiety (mean (SD))	0.00 (1.02)	0.00 (1.01)	0.004
PRS for bipolar disorder (mean (SD))	-0.18 (0.99)	-0.15 (0.99)	0.026
PRS for schizophrenia (mean (SD))	-0.26 (0.93)	-0.21 (0.95)	0.050
PRS for ADHD (mean (SD))	-0.11 (0.96)	-0.08 (0.97)	0.033

[b] Each PRS was standardized across the full All of Us Research Program sample prior to analyses. SNRI, serotonin and norepinephrine reuptake inhibitor; SD, standard deviation; SSRI, serotonin reuptake inhibitor; SD, standard deviation; PTSD, post-traumatic stress disorder; ADHD, attention deficit-hyperactivity disorder; PRS, polygenic risk score.



(a) SSRIs vs. bupropion.

(b) SSRIs vs. SNRIs.

Figure 1: Kaplan-Meier curves of suicidal thoughts.

Subgroup analyses reveal effect heterogeneity across ADHD PRS

We conducted subgroup analyses to evaluate the heterogeneity in the risks of suicidal thoughts associated with antidepressant use across demographic characteristics, clinical characteristics, and PRSs. In the comparison bewteen SSRIs and bupropion, participants generally had similar hazard ratios across nongenetic characteristics (Figure 2). Participants with PRS for ADHD higher than the median had a hazard ratio of 1.66 (95%CI, 1.30 to 2.12), while participants with PRS for ADHD lower than the median had a hazard ratio of 1.06 (95%CI, 0.81 to 1.38; P-for-interaction, 0.01). We observed a similar trend for schizophrenia: participants with PRS for schizophrenia higher than the median had a hazard ratio of 1.52 (95%CI, 1.19 to 1.93), while participants with PRS for schizophrenia lower than the median had a hazard ratio of 1.17 (95%CI, 0.89 to 1.53; P-for-interaction, 0.16; Figure 2).

In the comparison between SSRIs and SNRIs, males had a hazard ratio of 1.31 (95%CI, 1.04 to 1.65), while other genders had a hazard ratio of 0.86 (95%CI, 0.70 to 1.05; P-for-interaction, 0.01). Hazard ratios were similar across PRSs, with all PRS subgroups having treatment effects close to the null (Figure 3).

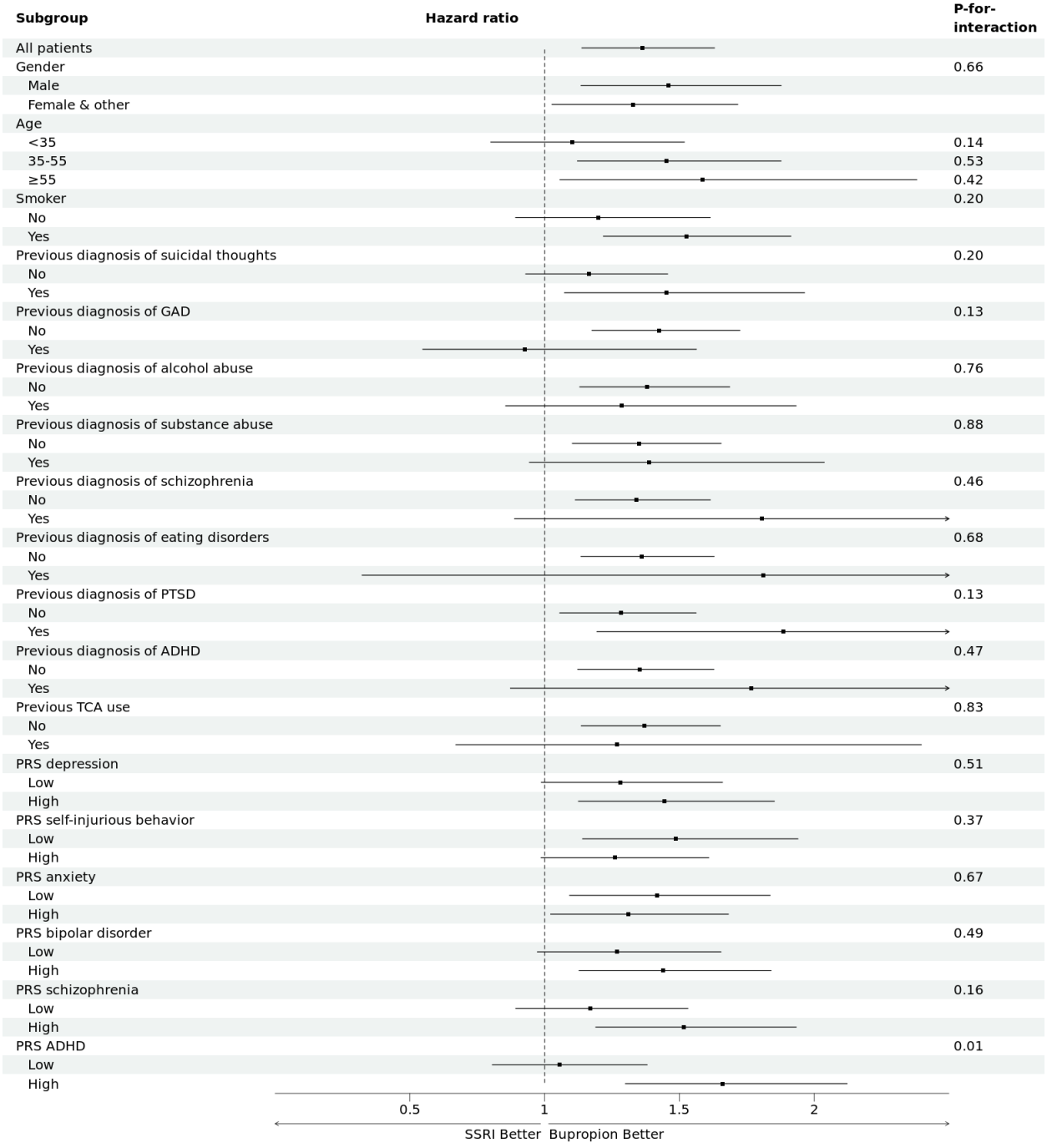


Figure 2: Subgroup analyses for SSRIs vs. bupropion.

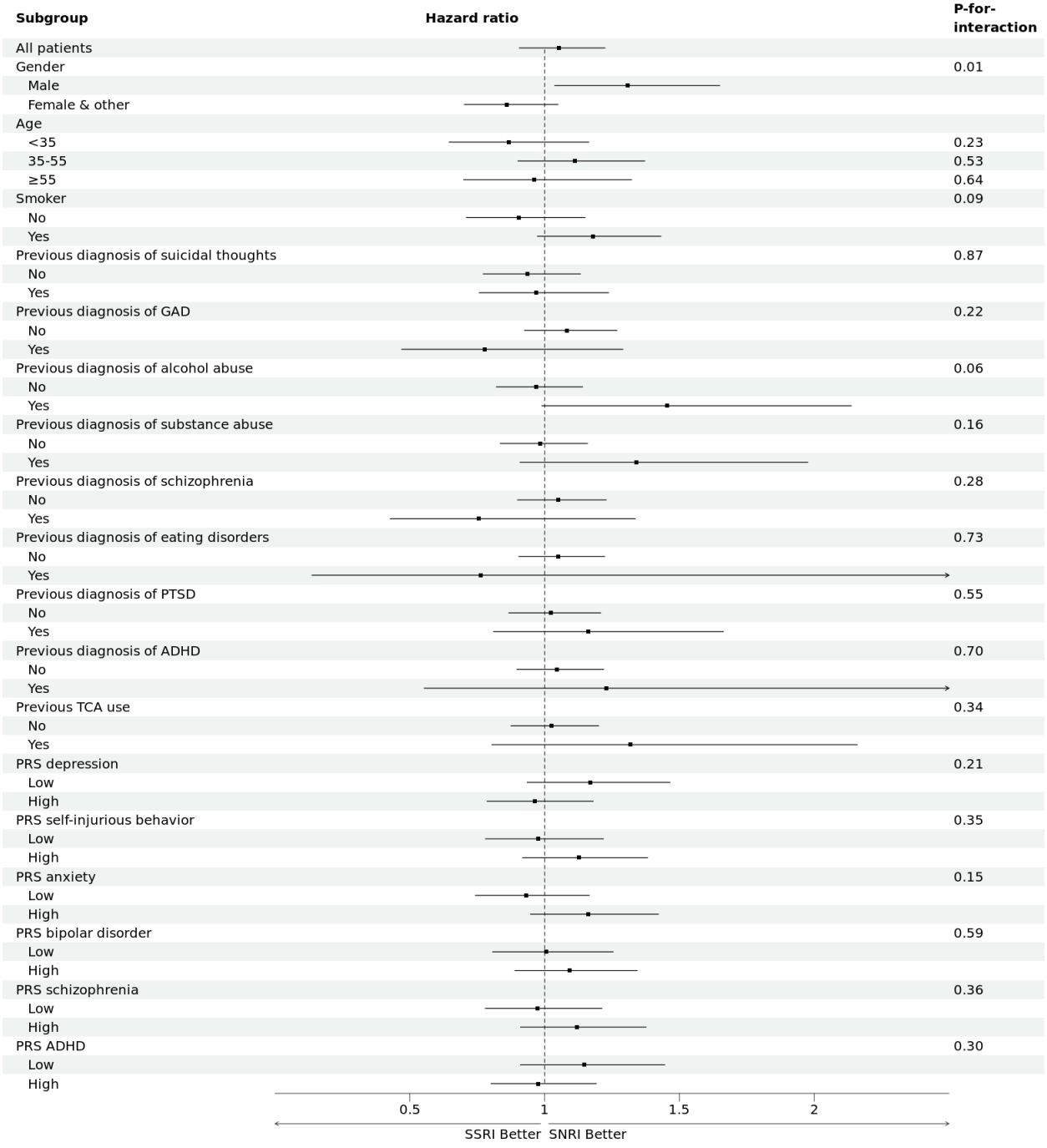
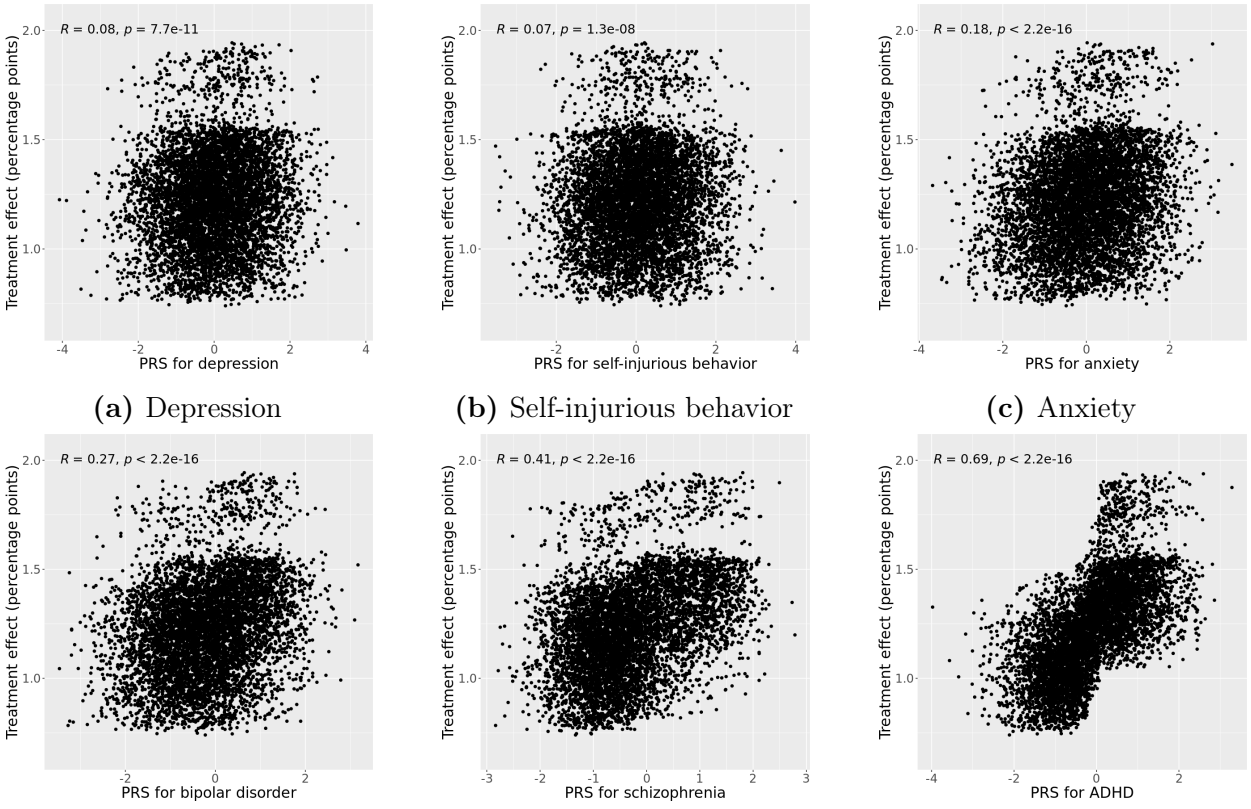


Figure 3: Subgroup analyses for SSRIs vs. SNRIs.

Machine learning causal forest highlights nonlinear effect heterogeneity across PRSs for psychiatric disorders

We estimated the conditional average treatment effects (CATEs) of antidepressants on suicidal thoughts by constructing causal forest models. These models allow us to elucidate nonlinear relationships between each individual's characteristics and the estimated effects of antidepressants on suicidal thoughts. The causal forest model for SSRIs vs. bupropion showed good calibration. There was heterogeneity in the treatment effect on suicidal thoughts based on the best linear projection of CATEs (Extended Data Table 2) [19] and in the plots of CATEs in quintiles (Extended Data Figure 7). The causal forest model for SSRIs vs. SNRIs had poor calibration (Extended Data Table 3). Thus, we proceeded with the evaluation of treatment effect heterogeneity across PRSs using the causal forest model for SSRIs vs. bupropion. There was a positive correlation between CATEs of SSRIs relative to bupropion and PRSs for psychiatric disorders, particularly for ADHD and schizophrenia. Thus, CATEs were heterogeneous across PRSs for psychiatric disorders: the higher the PRS, the higher the risk of suicidal thoughts with SSRI use (Figure 4).



(a) Depression **(b)** Self-injurious behavior **(c)** Anxiety

(d) Bipolar disorder **(e)** Schizophrenia **(f)** ADHD

Figure 4: Conditional average treatment effects of SSRIs relative to bupropion across PRSs. Shown are Pearson correlation coefficients and P-values.

Discussion

We find evidence that bupropion may be less likely to elicit suicidal thoughts compared to SSRIs among individuals with high genetic predisposition for psychiatric disorders, particularly for ADHD. Notably, conventional subgroup analyses across nongenetic characteristics did not reveal heterogeneity in the risk of suicidal thoughts. These findings suggest that considering PRSs in the personalized medicine framework may help clinicians decide which antidepressant should be prescribed for each patient to avoid serious adverse effects such as suicidal thoughts.

Our finding that bupropion may be less likely to elicit suicidal thoughts among individuals with high ADHD PRS may result from the fact that bupropion improves ADHD symptoms [20], which includes impulsivity and hyperactivity, and supports the role of impulsivity in suicidal ideation and behavior [21]. Interestingly, we did not find that those who have received a previous diagnosis of ADHD had a lower risk of suicidality with bupropion use compared to those without an ADHD diagnosis. Thus, even if an individual has not clinically manifested ADHD symptoms, merely their genetic tendency to do so may guide clinical practice.

We did not find large heterogeneity in the effects of SSRIs relative to SNRIs across PRSs. Instead, we found that males may have lower risk of increased suicidal thoughts with SNRI (relative to SSRI) use compared to other genders. This is generally in agreement with previous RCTs, which suggest that females may respond better to antidepressants than males and that this trend is more evident for SSRIs than SNRIs [22], though direct comparisons between SSRIs and SNRIs are not well-documented. Thus, this gender difference may be a novel finding that warrants further investigation.

Thus far, it was unclear whether genetic information could guide personalized care for patients with depression. Though there have been associational studies on PRSs for various psychiatric diseases, decisionmaking in psychiatric care was, for the most part, based primarily on patients' clinical and sociodemographic characteristics and not on their genetic information. Furthermore, even when genetic information is available, few large scale databases have both clinical and genetic data that can evaluate its utility in predicting the adverse events of antidepressants. Combining clinical and genetic information on a large sample of antidepressant users from the All of Us Research Program, the present study filled this knowledge gap on the utility of genetic information in personalized psychiatric care: at least for minimizing suicidal thoughts, PRSs are likely useful in personalizing pharmacotherapy for depression. Investigating this further may provide a better picture of the pathophysiology and subtyping of depression and comorbidities, with which we can further advance personalized psychiatry.

Our study should be interpreted in light of several limitations. First, the PRSs had limited performance in predicting each psychiatric disorder, especially for minoritized populations (though they were comparable to their performance described in their respective original studies). Although this is beyond the scope of the exploratory nature of our study (in addition to the fact that the development of PRSs was not an objective of this study), attempts to improve PRS performance among the general and minoritized populations, such as the one by Lennon and others [23], may be warranted. Second, there may have been misclassification, especially for self-reported variables such as education level, annual income, health insurance

coverage, birthplace, and smoking status. Third, participants in the All of Us Research Program may not be generalizable to the general population, as the program obtains data only from patients in registered facilities. Finally, there may have been unmeasured confounding by factors not evaluated in the All of Us Research Program, such as individuals' clinical, sociodemographic, or molecular profiles.

In conclusion, among individuals with major depressive disorder, we detect substantial heterogeneity in the risk of suicidal thoughts with antidepressant use across polygenic risk scores for psychiatric disorders. Considering PRSs for various psychiatric disorders may help clinicians tailor antidepressants to each patient to avoid serious adverse effects such as suicidal thoughts.

Methods

Study design and data

We aimed to emulate a randomized controlled trial (RCT) to evaluate the effect of antidepressants on suicidal thoughts among patients with major depressive disorder, as well as the heterogeneity in the effects across PRSs for several psychiatric disorders and clinical characteristics of patients. To emulate this hypothetical RCT, we used data from the All of Us Research Program, a large National Institutes of Health-led longitudinal cohort of a diverse sample of the US population [18].

The All of Us Research Program combines participant-derived information from surveys, electronic health records, and biospecimens (including whole genome sequences of blood samples), among other sources, and launched its national recruitment in May 2018. As of 2024, more than 835,000 participants have been enrolled, of whom more than 588,000 had provided biospecimens. Short-read whole genome sequences were available for more than 245,000 of these participants. Enrollment centers are from various settings, including health provider organizations and community partners, with emphasis on recruiting participants from groups historically underrepresented in biomedical research.

All analyses were conducted on the All of Us Researcher Workbench, a cloud-based platform that allows researchers to perform data extraction, curation, and analyses. No individual-level data were downloaded onto a local computer.

Target trial emulation

We used the target trial emulation framework [17] to emulate a RCT using observational data to obtain treatment effect estimates with minimal bias. We used an active-comparator design for drug effect comparison [24] to align the timings of eligibility evaluation, intervention, and the initiation of the follow-up period. The follow-up period started at treatment assignment and ended at the occurence of the outcome or at five years from treatment assignment, whichever occurred first. All individuals with a diagnosis of major depressive disorder and with available outcome, treatment, and covariate data, including genomic data, available were eligible for matching.

Each participant in the treatment group was matched without replacement to the control group at a 1-to-1 ratio. We used propensity scores to match the participants, with a caliper of 0.10. Propensity scores were calculated by constructing logistic regression models of the treatment using all covariates, and the matched treatment and control samples were compared by calculating the standardized mean differences (SMDs) for each covariate. We included a square term of age in the propensity score model to obtain adequate balance between the covariates. Data on all participants meeting the inclusion criteria were used to construct the models, meaning some participants in the propensity score models were not included in the final matched sample. Matching was performed sequentially in chronological order of the month of antidepressant initiation and was done separately for each month. The order of matching of participants with the same month of antidepressant initiation was chosen at random.

Variable extraction

Data for all variables were extracted from the All of Us Researcher Workbench. The All of Us Research Program records different diseases and drugs based on the codes in each participating hospital. The codes are thus not uniform: one patient may have a disease coded in International Classification of Disease (ICD)-10, while another may have a disease coded in ICD-9. Thus, the All of Us Research Program uses the Systematized Nomenclature of Medicine (SNOMED) [25] to match up these disease codes. Similarly, the All of Us Research Program records drugs using RxNorm [26], which codes all medications available on the US market. We manually surveyed all SNOMED and RxNorm keywords related to the diseases and drugs of interest in the All of Us Research Program, and chose relevant SNOMED and RxNorm keywords for each disease or drug, as well as the dates they were recorded. The keywords we used are available as Supplementary Information. All other variables, including sociodemographic variables, were recorded via a survey by the All of Us Research Program.

This study sought to emulate a RCT that performs comparisons of two pairs of antidepressants: SSRIs vs. bupropion, and SSRIs vs. SNRIs. In both comparisons, treatment effects were estimated with SSRIs as the treatment and the other drug as the control.

Participants were allocated into the treatment or control group based on whichever drug was initiated first. For instance, if an individual was started on SSRIs and was later given SNRIs, the individual was classified into the SSRI group. Thus, all analyses of treatment effects were intention-to-treat analyses. If an individual was given both drugs on the same date, they were excluded from the analyses.

The outcome of interest was suicidal thoughts, as recorded in electronic health records. As suicidal ideation is most common with the initiation of antidepressants, we did not evaluate the long-term effects of antidepressants, and the outcome was censored at five years.

We included the following covariates obtained from self-reported surveys in the matching process and evaluation of effect heterogeneity: gender (female, male, or other), age, race and ethnicity (Non-Hispanic Black, Non-Hispanic White, Hispanic, or other), education level (Whether they attended college), annual income (less than $25,000, $25,000 to $50,000, $50,000 to $100,000, or more than $100,000), health insurance coverage, birthplace (US

or other), and smoking status (at least 100 cigarettes in one's lifetime or not). All survey variables were recorded at the time of recruitment into the All of Us Research Program, regardless of the timing of drug initiation.

We also included the previous diagnoses of suicidal thoughts, generalized anxiety disorder, alcohol abuse, schizophrenia, eating disorders, post-traumatic stress disorder (PTSD), and ADHD, as well as the previous use of tricyclic antidepressants. Here, a previous diagnosis or previous use of drug was defined as the coding of the disease or drug in the electronic health record any time before the initiation of the drug of interest. We did not include the previous diagnosis of any other mood disorders.

We included PRSs for depression, self-injurious behavior, bipolar disorder, schizophrenia, anxiety, and attention deficit-hyperactivity disorder (ADHD) as covariates. These were chosen based on previous literature on potential associations between PRSs and treatment effect heterogeneity of antidepressants and psychiatric disorders that have genetic overlap with depression [10, 12, 14, 15], as well as the availability of each PRS on PGS catalog. Of note, the PRS for anxiety included not only generalized anxiety disorder but also panic disorder (episodic paroxysmal anxiety), mixed anxiety and depressive disorder, other mixed anxiety disorders, other specified anxiety disorders, and anxiety disorder, unspecified.

We obtained whole genome sequences from each participant and calculated their PRS using weights from selected PRSs from the PGS catalog. Each PRS was standardized across the full All of Us Research Program sample prior to analyses. For each PRS, we calculated the Nagelkerke's R-squared value and area under the ROC (AUROC), for the full All of Us Research Program sample and by race and ethnicity. Evaluation of PRSs were performed using all available participant data; i.e., all participants with available PRSs and outcomes, even if they did not meet the inclusion criteria for the evaluation of treatment effects, were included.

Statistical analysis

First, we first compared the risks of suicidal thoughts between SSRI users and bupropion users and between SSRI users and SNRI users by plotting a Kaplan-Meier curve. In addition, we fit Cox proportional hazard models to estimate hazard ratios and 95% confidence intervals (CIs) for the outcome events.

Second, we conducted subgroup analyses to evaluate the heterogeneity in the risks of suicidal thoughts associated with antidepressant use across demographic and clinical characteristics as well as PRSs. Gender was dichotomized as the number of individuals reporting to be neither male nor female were small. Age was trichotomized to group the participants into roughly same subsamples and to capture the possibility that antidepressants respond differently among young populations. PRSs were dichotomized at the median for better interpretability. P-values were calculated for the coefficients of the interaction terms between the treatment and covariates of interest.

Finally, we estimated the conditional average treatment effects (CATEs), treatment effect conditional on multi-dimensional characteristics for each individual such as demographic characteristics, previous diagnoses, and PRSs, by constructing causal forest models [27, 28]

to capture the nonlinearity in the treatment effect heterogeneity across PRSs. As with the average treatment effect estimation, a separate causal forest model was constructed for each comparison (SSRIs vs. bupropion and SSRIs vs. SNRIs). The outcome used was suicidal thoughts within three years of drug initiation. We constructed the causal forest models with all covariates, using cross-fitting with 10 folds. We evaluated the calibration of the models using the best linear projection of CATEs [19] and by ranking the CATEs into quintiles within each of the folds, calculating the average treatment effect of individuals in each quintile with the model and comparing them with ordinary least squares estimates. A model with good calibration will have average treatment effects within each quintile similar to the ordinary least squares estimates, and the average treatment effects will increase incrementally. We evaluated the treatment effect heterogeneity across individuals' PRSs for each of the psychiatric disorders by plotting their CATEs across their PRSs [29], and calculated Spearman correlation coefficients between CATEs and PRSs as well as their P-values.

Ethical considerations

The All of Us Research Program has been approved by the All of Us Institutional Review Board. As the Program follows a "passport model" that grants broad access to the research dataset approved by the program institutional review board instead of the institutional review board at researchers' affiliations, the present study was exempt from obtaining ethical approval from authors' institutions. All researchers who access the All of Us Research Program data are authorized and approved via a process that includes registration, affiliation with an institution that has completed a Data Use and Registration Agreement, identity verification, completion of ethics training, and attestation to a data use agreement. Results reported comply with the All of Us Data and Statistics Dissemination Policy that prohibits disclosure of group counts under 20 to protect participant privacy.

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Acknowledgements

We gratefully acknowledge All of Us participants for their contributions, without whom this research would not have been possible. We also thank the National Institutes of Health's All of Us Research Program for making available the participant data and/or samples examined in this study.

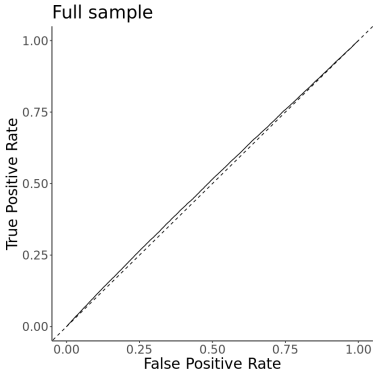
Funding

R.G. receives funding from Knight-Hennessy Scholars, the Japan Foundation for Pediatric Research (22-001), and Chernobyl-Fukushima Medical Foundation for other work not related to this study. K.I. receives research support from the Japan Society for the Promotion of Science (23KK0240), the Japan Agency for Medical Research and Development (AMED; JP22rea522107), the Japan Science and Technology (JST PRESTO; JPMJPR23R2), and the Program for the Development of Next-generation Leading Scientists with Global Insight (L-INSIGHT) sponsored by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the

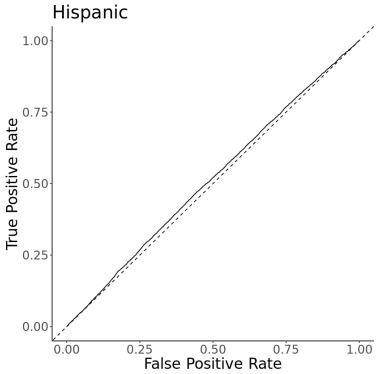
manuscript; and decision to submit the manuscript for publication.

The All of Us Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

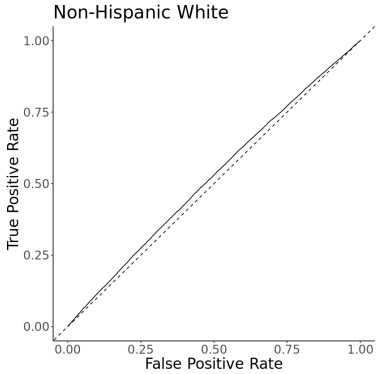
Extended Data Figures



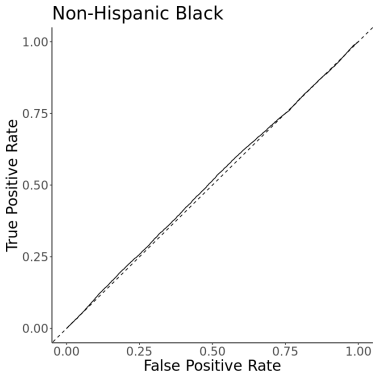
(a) Full sample. AUC=0.510, Nagelkerke's R^2=0.000291.



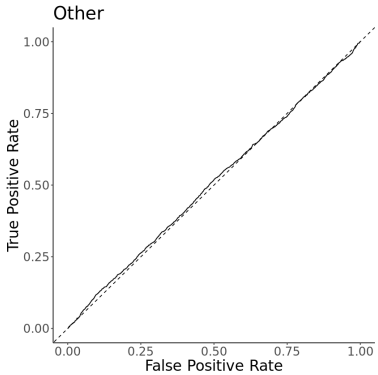
(b) Hispanic. AUC=0.514, Nagelkerke's R^2=0.000541.



(c) Non-Hispanic White. AUC=0.521, Nagelkerke's R^2=0.00129.

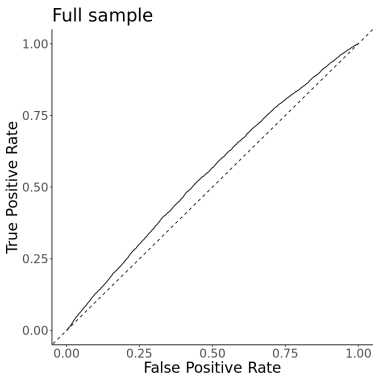


(d) Non-Hispanic Black. AUC=0.508, Nagelkerke's R^2=0.000128.

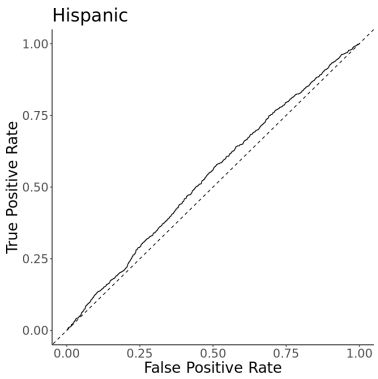


(e) Other. AUC=0.506, Nagelkerke's R^2=6.49×10^{-5}.

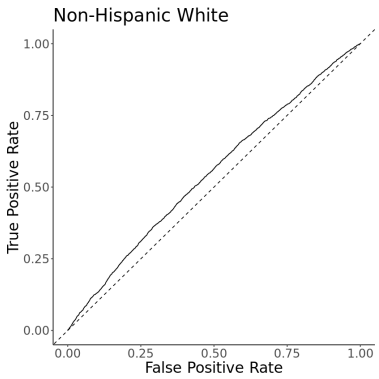
Extended Data Figure 1: ROC curves of PRS for depression.



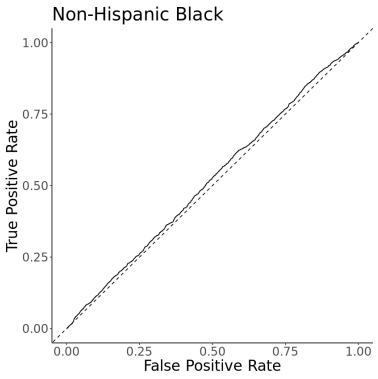
(a) Full sample. AUC=0.547, Nagelkerke's R^2=0.00324.



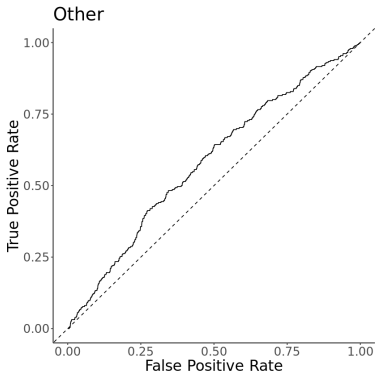
(b) Hispanic. AUC=0.537, Nagelkerke's R^2=0.00185.



(c) Non-Hispanic White. AUC=0.546, Nagelkerke's R^2=0.00315.

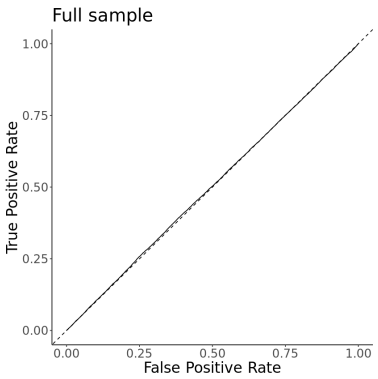


(d) Non-Hispanic Black. AUC=0.518, Nagelkerke's R^2=0.000586.

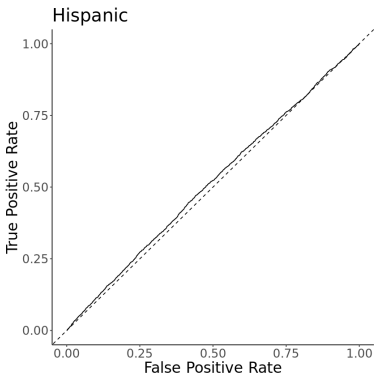


(e) Other. AUC=0.582, Nagelkerke's R^2=0.00772.

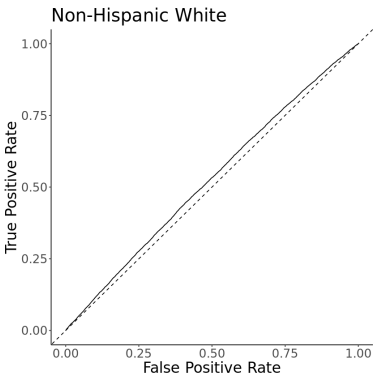
Extended Data Figure 2: ROC curves of PRS for suicidal thoughts.



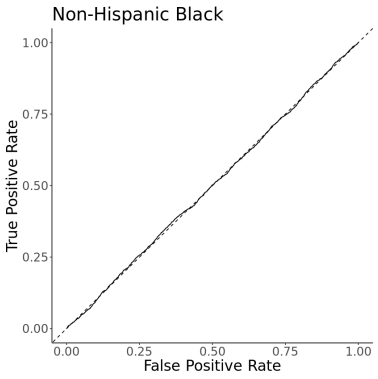
(a) Full sample. AUC=0.502, Nagelkerke's R^2=3.58×10^{-6}.



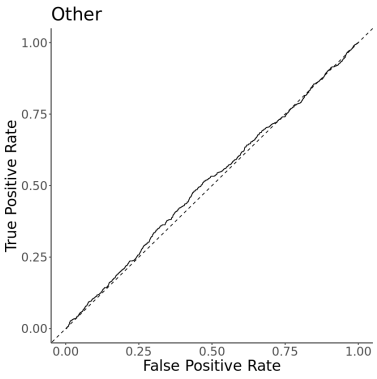
(b) Hispanic. AUC=0.514, Nagelkerke's R^2=0.000300.



(c) Non-Hispanic White. AUC=0.524, Nagelkerke's R^2=0.00126.

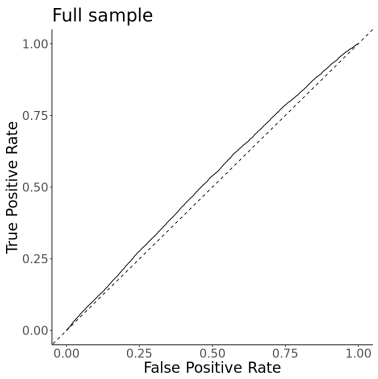


(d) Non-Hispanic Black. AUC=0.501, Nagelkerke's R^2=3.64×10^{-6}.

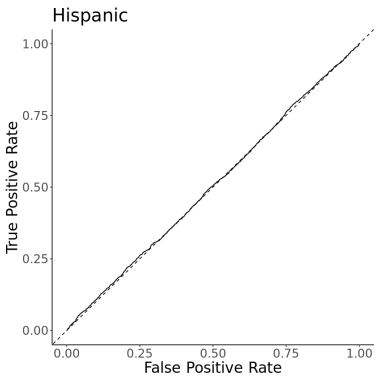


(e) Other. AUC=0.513, Nagelkerke's R^2=0.000233.

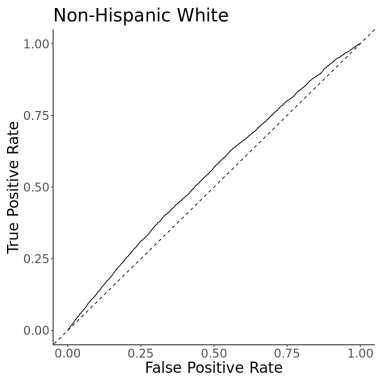
Extended Data Figure 3: ROC curves of PRS for anxiety.



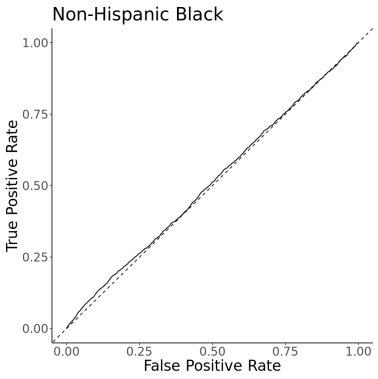
(a) Full sample. AUC=0.527, Nagelkerke's R^2=0.00134.



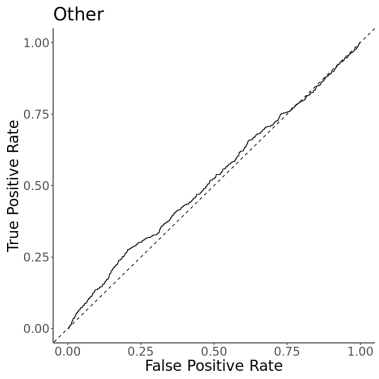
(b) Hispanic. AUC=0.504, Nagelkerke's $R^2=4.15 \times 10^{-5}$.



(c) Non-Hispanic White. AUC=0.548, Nagelkerke's R^2=0.00394.

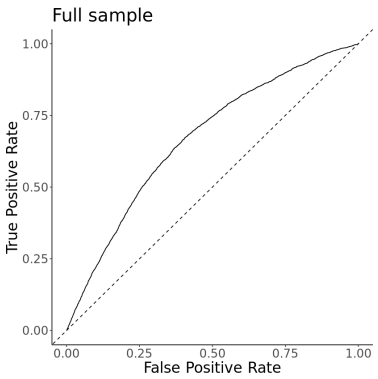


(d) Non-Hispanic Black. AUC=0.509, Nagelkerke's R^2=0.000229.

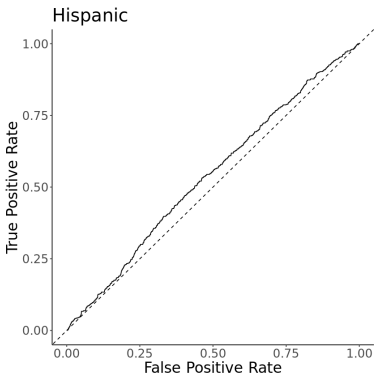


(e) Other. AUC=0.523, Nagelkerke's R^2=0.00728.

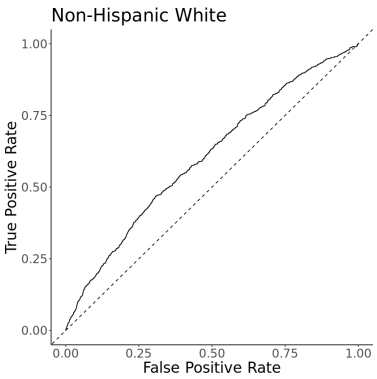
Extended Data Figure 4: ROC curves of PRS for bipolar disorder.



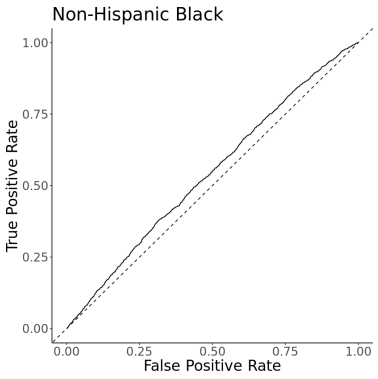
(a) Full sample. AUC=0.668, Nagelkerke's R^2=0.0340.



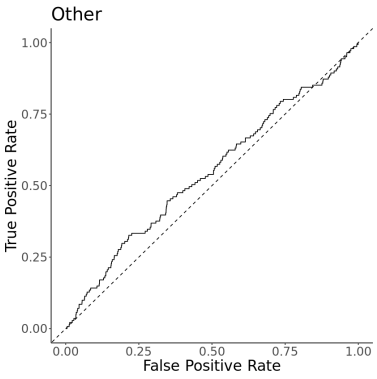
(b) Hispanic. AUC=0.538, Nagelkerke's R^2=0.00164.



(c) Non-Hispanic White. AUC=0.603, Nagelkerke's R^2=0.0118.

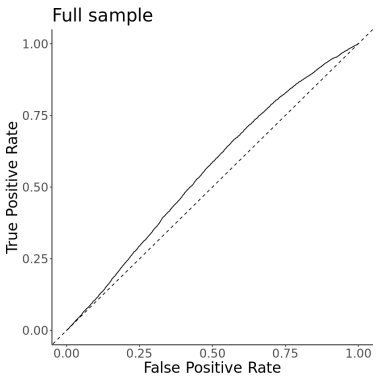


(d) Non-Hispanic Black. AUC=0.541, Nagelkerke's R^2=0.00273.

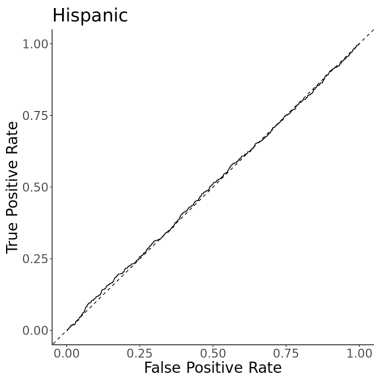


(e) Other. AUC=0.545, Nagelkerke's R^2=0.00148.

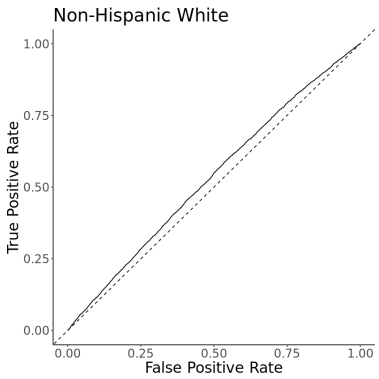
Extended Data Figure 5: ROC curves of PRS for schizophrenia.



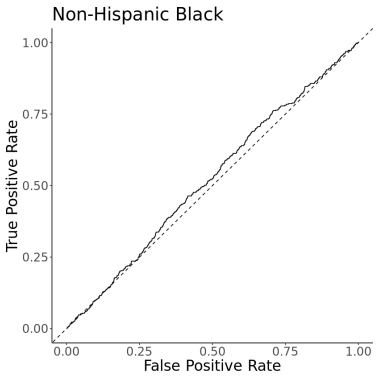
(a) Full sample. AUC=0.554, Nagelkerke's R^2=0.00368.



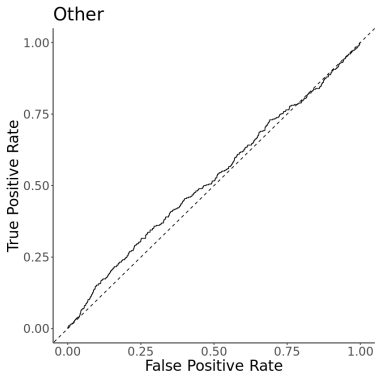
(b) Hispanic. AUC=0.504, Nagelkerke's $R^2=1.36 \times 10^{-5}$.



(c) Non-Hispanic White. AUC=0.533, Nagelkerke's R^2=0.00167.

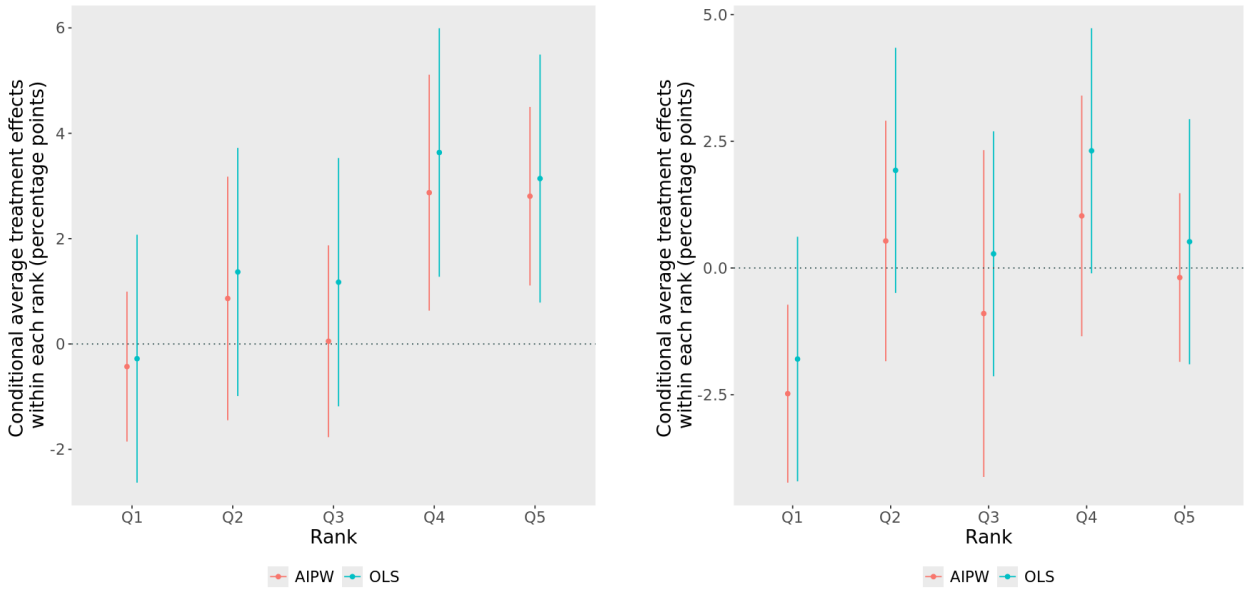


(d) Non-Hispanic Black. AUC=0.521, Nagelkerke's R^2=0.000401.



(e) Other. AUC=0.526, Nagelkerke's R^2=0.000940.

Extended Data Figure 6: ROC curves of PRS for ADHD.



(a) SSRIs vs. bupropion

(b) SSRIs vs. SNRIs

Extended Data Figure 7: Treatment effects for each quintile of CATEs.

Supplementary Information

Keywords for extracting disease and drug information

We used the following keywords to extract disease information:

- Major depressive disorder: contains "major depressive disorder" or "major depression"
- Suicidal thoughts: contains "thoughts of self harm" or "suicidal thoughts" or "planning suicide" or suicidal intent" or "thoughts of deliberate self harm"
- Generalized anxiety disorder: contains "generalized anxiety disorder"
- Bipolar disorder: contains "bipolar"
- Alcohol abuse: contains "alcohol abuse"
- Substance abuse: contains "amphetamine abuse" or "cocaine abuse" or "cannabis abuse"
- Schizophrenia: contains "schizophrenia"
- Eating disorders: contains "anorexia nervosa" or "bulimia nervosa"
- Post-traumatic stress disorder: contains "posttraumatic stress disorder" or "post-traumatic stress disorder"
- Attention deficit-hyperactivity disorder: contains "attention deficit hyperactivity disorder"

We used the following keywords to extract drug information:

- Selective serotonin reuptake inhibitors: contains "citalopram" or "escitalopram" or "fluoxetine" or "fluvoxamine" or "paroxetine" or "sertraline"
- Serotonin and norepinephrine reuptake inhibitors: contains "desvenlafaxine" or "duloxetine" or "milnacipran" or "venlafaxine"
- Bupropion: contains "bupropion"
- Tricyclic antidepressants: contains "amitriptyline" or "amoxapine" or "clomipramine" or "desipramine" or "doxepin" or "imipramine" or "maprotiline" or "nortriptyline" or "protriptyline" or "trimipramine"

Supplementary Tables

Supplementary Table 1: Traits, polygenic score ID, and URL of the polygenic risk scores

Trait	PRS ID	URL
Depression	PGS000145	https://www.pgscatalog.org/trait/MONDO_0002009/
Self-injurious behavior	PGS002222	https://www.pgscatalog.org/trait/HP_0100716/
Anxiety[c]	PGS004451	https://www.pgscatalog.org/trait/EFO_0006788/
Bipolar disorder	PGS002786	https://www.pgscatalog.org/trait/MONDO_0004985/
Schizophrenia	PGS002785	https://www.pgscatalog.org/trait/MONDO_0005090/
ADHD	PGS002746	https://www.pgscatalog.org/trait/EFO_0003888/

[c] Includes panic disorder (episodic paroxysmal anxiety), generalized anxiety disorder, mixed anxiety and depressive disorder, other mixed anxiety disorders, other specified anxiety disorders, and anxiety disorder, unspecified. PRS, polygenic risk score; ADHD, attention deficit-hypteractivity disorder.

Supplementary Table 2: Best linear projection of the conditional average treatment effects, SSRIs vs. bupropion

	Estimate	Standard error	P-value
Mean prediction[d]	1.00	0.41	0.007
Differential prediction[d]	0.59	3.16	0.43

Supplementary Table 3: Best linear projection of the conditional average treatment effects, SSRIs vs. SNRIs

	Estimate	Standard error	P-value
Mean prediction[d]	0.92	0.71	0.10
Differential prediction[d]	-3.07	1.57	0.97

[d] Mean prediction evaluates how well the causal forest model captures the average treatment effect, while differential prediction refers to how well the causal forest model captures the heterogeneity in the treatment effects across covariates. [19, 28]