Penetrance and Pleiotropy of Polygenic Risk Scores for Schizophrenia, Bipolar Disorder, and Depression Among Adults in the US Veterans Affairs Health Care System

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IMPORTANCE Serious mental illnesses, including schizophrenia, bipolar disorder, and depression, are heritable, highly multifactorial disorders and major causes of disability worldwide.

OBJECTIVE To benchmark the penetrance of current neuropsychiatric polygenic risk scores (PRSs) in the Veterans Health Administration health care system and to explore associations between PRS and broad categories of human disease via phenome-wide association studies.

DESIGN, SETTING, AND PARTICIPANTS Extensive Veterans Health Administration’s electronic health records were assessed from October 1999 to January 2021, and an embedded cohort of 9378 individuals with confirmed diagnoses of schizophrenia or bipolar 1 disorder were found. The performance of schizophrenia, bipolar disorder, and major depression PRSs were compared in participants of African or European ancestry in the Million Veteran Program (approximately 400,000 individuals), and associations between PRSs and 1650 disease categories based on ICD-9/10 billing codes were explored. Last, genomic structural equation modeling was applied to derive novel PRSs indexing common and disorder-specific genetic factors. Analysis took place from January 2021 to January 2022.

MAIN OUTCOMES AND MEASURES Diagnoses based on in-person structured clinical interviews were compared with ICD-9/10 billing codes. PRSs were constructed using summary statistics from genome-wide association studies of schizophrenia, bipolar disorder, and major depression.

RESULTS Of 707,299 enrolled study participants, 459,667 were genotyped at the time of writing; 84,806 were of broadly African ancestry (mean [SD] age, 58 [12.1] years) and 314,909 were of broadly European ancestry (mean [SD] age, 66.4 [13.5] years). Among 9378 individuals with confirmed diagnoses of schizophrenia or bipolar 1 disorder, 8962 (95.6%) were correctly identified using ICD-9/10 codes (2 or more). Among those of European ancestry, PRSs were robustly associated with having received a diagnosis of schizophrenia (odds ratio [OR], 1.81 [95% CI, 1.76-1.87]; P < 10^{-257}) or bipolar disorder (OR, 1.42 [95% CI, 1.39-1.44]; P < 10^{-295}). Corresponding effect sizes in participants of African ancestry were considerably smaller for schizophrenia (OR, 1.35 [95% CI, 1.29-1.42]; P < 10^{-38}) and bipolar disorder (OR, 1.16 [95% CI, 1.11-1.22]; P < 10^{-10}). Neuropsychiatric PRSs were associated with increased risk for a range of psychiatric and physical health problems.

CONCLUSIONS AND RELEVANCE Using diagnoses confirmed by in-person structured clinical interviews and current neuropsychiatric PRSs, the validity of an electronic health records-based phenotyping approach in US veterans was demonstrated, highlighting the potential of PRSs for disentangling biological and mediated pleiotropy.

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Serious mental illnesses such as schizophrenia, bipolar disorder, and major depression are leading causes of disability and public health expenditure, and affected persons disproportionately experience increased morbidity and early mortality. Recent years have seen important advances in our understanding of the complex multifactorial underpinnings of serious mental illnesses, with genome-wide association studies (GWAS) yielding robust and replicable associations with specific loci (270, 64, and 44 for schizophrenia, bipolar disorder, and major depression, respectively). However, small effect sizes at individual variants and extreme polygenicity have thwarted the transformative mechanistic insights needed for development of novel therapeutics and prevention strategies.

Polygenic risk scores (PRSs) aggregate genetic associations across the genome, including many variants that do not attain genome-wide significance and can account for more variance in liability than genome-wide significant findings alone, albeit they are typically less predictive than a positive family history or certain rare copy number variants. Ever-increasing GWAS sample sizes have seen the variance in liability captured by PRSs climb steadily, from 3% in the first demonstrative application to schizophrenia to upwards of 10% in recent Psychiatric Genomics Consortium analyses. As applied to nonpsychiatric traits, the clinical utility of PRSs is emergent, and potential applications in psychiatry are actively being explored, including risk stratification and predicting treatment response.

With large biobanks now linking the electronic health records (EHRs) of hundreds of thousands of patients to their individual-level genomic data, there are opportunities to explore the associations of PRSs (or specific variants) with a wide range of clinical phenotypes, i.e., a genotype-to-phenotype or reverse genetics paradigm. Also known as phenome-wide association studies (PheWAS), this unbiased, disease-agnostic approach has the potential to uncover hitherto unrecognized associations between distinct diagnostic entities and to aid in disentangling complex pleiotropic associations. A recent application of PheWAS from the PsycheMERGE Consortium analyzed schizophrenia PRSs in more than 100 000 patients from 4 large health care systems (Geisinger Health System, Mount Sinai Health System, Partners HealthCare System, and Vanderbilt University Medical Center) and uncovered robust associations with both psychiatric and nonpsychiatric diagnoses.

The Veterans Health Administration (VHA) is the largest integrated health care system in the United States, with 171 medical centers and 1112 outpatient clinics serving more than 9 million veterans. Launched in 2010, the Million Veteran Program (MVP) is a landmark endeavor that links genomic laboratory testing, survey-based self-report data, and EHRs spanning decades, with the goal of creating a mega-biobank and novel evidence base for precision medicine initiatives. Demographically and clinically, the 850 000 enrolled participants reflect the population that uses the VHA, with overrepresentation of older individuals and male individuals, as well as higher rates of multiple, chronic conditions compared with the general population, despite better access to health care.

### Findings

In this cross-sectional study of 707 299 individuals, PRSs were associated with having ever received a relevant psychiatric diagnosis and were enriched among more frequently hospitalized patients. Higher PRSs were associated with increased odds for numerous mental and physical health diagnoses, even among individuals who lack a formal diagnosis.

### Meaning

Individual-level PRSs informed by large-scale genetic studies are portable across US health care systems and have emergent potential for risk stratification, albeit with disparate specificity across ancestries.

### Methods

#### Study Participants

This study was approved by the Veterans Affairs (VA) Central Institutional Review Board, and all patients provided written informed consent. Additional details of study ascertainment and assessment are described elsewhere.

Cooperative Studies Program (CSP) #572 is a cohort of approximately 9300 veterans with schizophrenia or bipolar 1 disorder who received detailed in-person assessments of clinical diagnosis, functioning, and symptomatology. Within this companion study to the MVP, we evaluated the sensitivity of ICD-9/10 billing codes for schizophrenia, bipolar disorder, and major depression, applying case-control definitions of varying stringency and breadth of clinical phenotype (eg, schizophrenia vs any psychosis). We benchmarked the penetrance of current neuropsychiatric PRSs for schizophrenia, bipolar disorder, and major depression in 400 000 ancestrally diverse MVP participants and explored the broad associations of PRS with physical and mental health conditions with PheWAS. Finally, recognizing the considerable shared genetic basis of these disorders, we applied genomic structural equation modeling to derive common and disorder-specific latent genetic factors for comparative genomic analyses and explored pleiotropic associations of these latent factors with PheWAS.

#### Key Points

**Question** What is the penetrance of polygenic risk scores (PRSs) for schizophrenia, bipolar disorder, and major depression among US veterans who use the Veterans Health Administration health care system and what health problems are associated with having a higher polygenic burden?

**Findings** In this cross-sectional study of 707 299 individuals, PRSs were associated with having ever received a relevant psychiatric diagnosis and were enriched among more frequently hospitalized patients. Higher PRSs were associated with increased odds for numerous mental and physical health diagnoses, even among individuals who lack a formal diagnosis.

**Meaning** Individual-level PRSs informed by large-scale genetic studies are portable across US health care systems and have emergent potential for risk stratification, albeit with disparate specificity across ancestries.

#### Cooperative Studies Program (CSP) #572

Participants were recruited through their clinicians, posted notices at participating VA hospitals, and through word of mouth from January 2011 to January 2020. All patients received the Structured Clinical Interview for the DSM-5 and met lifetime DSM-IV criteria for schizophrenia (n = 3953) or bipolar 1 disorder (n = 5425). Patients with major neurologic illnesses or medical problems that could interfere with central nervous system function were excluded. Information from medical records, patients’ clinicians, or other informants were used, if needed, to confirm diagnoses. Diagnosed substance misuse...
was not an exclusion criterion, given some concerns about representativeness. Participants received a brief cognitive assessment and the University of California, San Diego, Performance-Based Skills Assessment, Brief version, a performance-based measure of everyday functional skills.  

MVP

Participants were active users of the VHA health care system and were recruited through invitational mailings or by MVP staff while receiving clinical care. Informed consent and authorization for Health Insurance Portability and Accountability Act were the only other inclusion criteria. Participants were recruited from January 2011 to January 2020. All participants completed a baseline survey, which includes information on demographic factors, health status, lifestyle habits, military experiences, medical history, and family history of specific illnesses and physical features; many also completed an optional lifestyle survey.  

At the time of manuscript submission, 4697 individuals (approximately 50% of CSP #572 and approximately 0.7% of MVP) were dually enrolled in both CSP #572 and MVP. CSP #572 and MVP participants were genotyped on the MVP 1.0 Axiom array (eMethods in Supplement 1). Participants were classified as being of African or European ancestry using the harmonized ancestry and race and ethnicity method, which combines information on genetic ancestry with self-identified race and ethnicity.

EHRs

For 9378 CSP #572 participants and 697,921 non-overlapping MVP enrollees, we extracted ICD-9/10 billing codes related to schizophrenia, bipolar disorder, and major depression (eTable 1 in Supplement 1) and prescription records for commonly prescribed antipsychotics, mood stabilizers, and antidepressants (eTable 2 in Supplement 1) from the VHA Corporate Data Warehouse.

We compared CSP #572 participants’ Structured Clinical Interview for the DSM–confirmed diagnoses with the ICD-9/10 codes recorded in their EHRs. Given the challenge of the differential diagnosis, for individuals with both schizophrenia and bipolar disorder codes, we took the mode of the 5 most recent entries as the prevailing diagnosis.

PRS Profiling

We constructed PRSs from published Psychiatric Genomics Consortium GWAS results, testing these for association with disease outcomes in the MVP cohort. Variants that met quality control filtering in both the training and target data sets were clumped in the appropriate 1000 Genomes Project phase 3 population (r² > 0.1; 500-kb window), excluding the major histocompatibility complex. For varying P value thresholds in each training data set (eMethods in Supplement 1), scores were constructed by summing the number of tested alleles weighted by their effect estimates (ie, the log of the allelic odds ratio). To better facilitate comparison of our results with those based on civilian cohorts, we used a similar approach to Zheutlin et al, including comparing results based on a recently developed bayesian framework that applies continuous shrinkage to test statistics, PRS-continuous shrinkage.

Genomic Structural Equation Modeling

We used genomic structural equation modeling to model the genetic covariance structure underlying schizophrenia, bipolar disorder, and major depression. Briefly, genomic structural equation modeling models the multivariate genetic architecture of complex traits by estimating individual single-nucleotide variants (SNVs; formerly, single-nucleotide polymorphisms or SNPs) associations on latent constructs, is robust to sample overlap and sample-size imbalance, and does not require individual-level genotypes. We estimated the SNV associations with a common factor (shared across disorders) as well as associations specific to each disorder (eMethods in Supplement 1).

PheWAS

We used PheWAS to explore the associations between neuropsychiatric PRSs and phenes representing groupings of associated ICD-9/10 billing codes. When testing individual phenes, we required individuals with these disorders and controls to have 2 or more and zero codes, respectively. We applied logistic regression to test scaled PRSs (mean [SD], 0 [1]) for association with phenes within ancestry groups, covarying for age, age², sex, and ancestry principal components.

We performed a series of sensitivity analyses, covarying for selected diagnoses or treatment with antipsychotics, mood stabilizers, and antidepressants, or removing individuals with any lifetime diagnosis of psychotic, mood, or substance disorders (eMethods in Supplement 1). Two-sided P values were statistically significant at 10⁻⁵. Analysis took place from January 2021 to January 2022.

Results

Participants

Of 707,299 enrolled study participants, 459,667 were genotyped at the time of writing; 84,806 were of broadly African ancestry (mean [SD] age, 58 [12.1] years), and 314,909 were of broadly European ancestry (mean [SD] age, 66.4 [13.5] years). Of 9378 individuals in CSP #572, 3953 (42%) had schizophrenia, bipolar disorder, and major depression (eTable 1 in Supplement 1); 5425 (58%) had bipolar 1 disorder (median [SD] age, 53 [11.5] years; 1005 [18.5%] female). There were 697,921 individuals in MVP (median [SD] age, 61 [14.2] years; 62,749 [9.0%] female). The Table and eTable 3 in Supplement 1 include descriptives for CSP #572 and MVP and display the number of participants meeting various case inclusion criteria based on phenes and medications.

Validation of EHR-Derived Phenotypes

We first sought to evaluate the precision and accuracy of EHR-derived phenotypes to capture caseness based on the Structured Clinical Interview for the DSM-based diagnoses available in CSP #572. Among 9378 patients, 8962 (95.6%) were correctly assigned using 2 or more relevant phenes.

Overall, 1153 of 3953 confirmed patients with schizophrenia (29.2%) had 2 or more bipolar disorder–related phenes, and 1869 of 5425 confirmed patients with bipolar 1 disorder...
The best overall balance of sensitivity vs specificity (Table, we concluded that a minimum of 2 phecodes offered
1.60 \[95\% CI, 1.22-2.11\];

-0.09\[95\% CI, –0.13 to –0.06\];

California, San Diego, Performance-Based Skills Assessment,

Penetrance of Neuropsychiatric PRS

2.24 \[95\% CI, 1.83-2.74\]; P < 10^{-14}\;

Brief version scores (β = –0.09\[95\% CI, –0.13 to –0.06\];

Paranoid

<1 0−14), male (OR, 1.26-1.45; P < 10^{-16}).

Cross-Ancestry Portability of Neuropsychiatric PRS

The prevalence of bipolar disorder in the top 10% had 1.7 times (95% CI, 1.61-1.75; P < 10^{-12}) higher likelihood to be
diagnosed with bipolar disorder.

Premature of bipolar disorder in the top and bottom bipolar disorder PRS deciles were 8.7% and 3.7%, equivalent
to a 2.5-fold (95% CI, 2.34-2.71; P < 10^{-15}) increase in risk. Compared with the bottom 90%, individuals in the top 10% had
1.7 times (95% CI, 1.61-1.75; P < 10^{-12}) higher likelihood to be
diagnosed with bipolar disorder.

The prevalence of major depression were 45% in the top PRS
decile and 34% in the bottom decile, corresponding to 1.7-
fold difference in risk (95% CI, 1.55-1.94; P < 10^{-21}). Comparing
the top 10% with the individuals in the remaining 90%, we observed an approximately 1.4-fold increase in risk (95% CI, 1.26-1.45; P < 10^{-16}).

Comparing receiver operating characteristic curves for pre-
dictive models based on the varying criteria displayed in the
Table, we concluded that a minimum of 2 phecodes offered the
best overall balance of sensitivity vs specificity (Figure 1;
eTable 6 in Supplement 1).

Penetration of Neuropsychiatric PRS in the VA Health Care System

Benchmarking results for neuropsychiatric PRSs based on varying P value thresholds are given in eTables 7 to 9 in Supple-
ment 1. Case prevalence estimates for each decile of PRS, re-
presenting the absolute disease prevalence, are displayed in Figure 2. As expected, the prevalence of serious mental ill-
esses was higher among veterans treated at VHA facilities than
in the general population.21,22

The prevalence of schizophrenia among participants of Eu-
ropean ancestry in the top and bottom deciles of schizophrenia
PRS was 4% and 0.9%, respectively, corresponding to 4.8-fold
higher odds (95% CI, 4.22-5.43; P < 10^{-15}). Individuals in the top
decile had approximately 2.4-fold higher odds of being diag-
osed with schizophrenia than those below the 90% percentile
(95% CI, 2.26-2.55; P < 10^{-183}); 2-fold higher odds for psychosis
(phecode 295.3) (95% CI, 1.85-2.09; P < 10^{-10}); 1.6-fold higher odds for bipolar disorder (95% CI, 1.53-1.66; P < 10^{-106}); and 1.2-
fold (95% CI, 1.15-1.21; P < 10^{-35}) for major depression.

The prevalence of bipolar disorder was between 5.8% and 6.8%,
respectively, in the top 10%. In contrast, across bipolar disorder PRS deciles, the absolute prevalence of bipolar
disorder was between 5.8% and 6.8%.

Individuals of African ancestry in the top decile of schizophrenia
PRSs had approximately 1.4-fold higher risk of diagnoses of

### Table. Cooperative Studies Program (CSP) #572 and Million Veteran Program (MVP) Participants Meeting Varying Electronic Health Records–Based Criteria for Schizophrenia, Bipolar Disorder, and Major Depression

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Phocode</th>
<th>Schizophrenia</th>
<th>Bipolar 1 disorder</th>
<th>Major Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>±1 ICD-9/10</td>
<td>±2 ICD-9/10</td>
<td>Inpatient</td>
<td>±1 ICD-9/10</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>295.1</td>
<td>3803 (96.2)</td>
<td>3770 (95.4)</td>
<td>2976 (75.3)</td>
</tr>
<tr>
<td>Paranoid</td>
<td>295.2</td>
<td>+8 (0.2)</td>
<td>+11 (0.3)</td>
<td>+9 (0.2)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>295.3</td>
<td>+26 (0.66)</td>
<td>+39 (1.0)</td>
<td>+64 (1.6)</td>
</tr>
<tr>
<td>Total</td>
<td>NA</td>
<td>3837 (97.1)</td>
<td>3820 (96.6)</td>
<td>3051 (77.2)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>296.1</td>
<td>610 (15.4)</td>
<td>462 (11.7)</td>
<td>189 (4.8)</td>
</tr>
<tr>
<td>(mania)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>296.1</td>
<td>+1063 (26.9)</td>
<td>691 (17.5)</td>
<td>+613 (15.5)</td>
</tr>
<tr>
<td>(any)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>NA</td>
<td>1673 (42.3)</td>
<td>1153 (29.2)</td>
<td>802 (20.3)</td>
</tr>
<tr>
<td>Depression</td>
<td>296.2</td>
<td>2997 (75.8)</td>
<td>2506 (63.4)</td>
<td>1529 (38.7)</td>
</tr>
<tr>
<td></td>
<td>±1 Rx</td>
<td>±2 Trials</td>
<td>±1 Rx</td>
<td>±2 Trials</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>3784 (95.7)</td>
<td>3413 (86.3)</td>
<td>4793 (88.4)</td>
<td>3816 (70.3)</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>1834 (46.4)</td>
<td>706 (17.9)</td>
<td>4854 (89.5)</td>
<td>3319 (61.2)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2928 (74.1)</td>
<td>1921 (48.6)</td>
<td>4529 (83.5)</td>
<td>3446 (63.5)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; Rx, prescription.

* Participants dually enrolled in CSP #572 and MVP were excluded.
schizophrenia than those below the 90% percentile (95% CI, 1.34-1.57; \(P < 10^{-18}\)) and 2.2-fold higher risk than those in bottom decile (95% CI, 1.89-2.65; \(P < 10^{-19}\)). At extremes, odds of bipolar disorder and major depression were increased 1.6-fold (95% CI, 1.33-1.84; \(P < 10^{-7}\)) and 1.3-fold (95% CI, 1.17-1.39; \(P < 10^{-7}\)), respectively.

**Schizophrenia PRS Have Equivalent Relative Penetrance in Civilian and Veteran Health Care Systems**

The demographics of the US veteran population differ from cohorts recruited from civilian health care systems. For instance, the VA population is composed of mostly male individuals (approximately 90%) and has higher prevalence of neuropsychiatric illnesses.\(^{23}\) Using the same training GWAS and bayesian PRS\(^{19}\) approach as used by the PsycheMERGE consortium,\(^{10}\) we see a robust association of schizophrenia PRSs with schizophrenia diagnosis (OR per SD-unit increase, 1.56 [95% CI, 1.52-1.61]; \(P = 2.7 \times 10^{-222}\)) in the European ancestry subset of our cohort, which is within the confidence interval estimated in the PsycheMERGE study (OR per SD-unit increase, 1.55 [95% CI, 1.39-1.72]).\(^{10}\) That is, despite stark differences in absolute prevalence between these cohorts, estimates of relative risks did not differ substantively.

**Higher Loadings of Neuropsychiatric PRS in More Chronic Illness**

We observed a trend of increased polygenic loading in more chronic illness presentations.\(^{1,24}\) Patients who received inpa-
tient treatment for schizophrenia had significantly higher PRS than those who did not (OR per SD-unit increase, 1.25 [95% CI, 1.18-1.34]; \( P < 10^{-11} \)); among these individuals, schizophrenia PRS was positively associated with number of hospitalizations (\( \beta = 0.198 \) [95% CI, 0.11-0.28]; \( P < 10^{-5} \)), including after adjusting for individuals’ total number of comorbidities (eMethods and eTables 10-13 in Supplement 1).

We observed similar patterns of results for bipolar disorder PRSs and number of hospitalizations (\( \beta = 0.14 \) [95% CI, 0.11-0.18]; \( P < 10^{-5} \)) (eTables 14-15 in Supplement 1). We investigated the apparent protective effects of schizophrenia PRSs by examining associations between individual genome-wide significant schizophrenia loci and selected phecodes (Figure 3), based on the same linkage disequilibrium–independent SNVs and analytic framework as used for PheWAS. Using a simple binomial test, we found that significantly more schizophrenia-associated SNVs than expected by chance (ie, 50%) had reversed directions of ass...
Citations with diabetes (168 of 270 [62.2%; 95% CI, 0.56-0.68]; \( P = 7.07 \times 10^{-5} \)), hearing loss (165 of 270 [61.1%; 95% CI, 0.55-0.67]; \( P = .000313 \)), and osteoarthritis (157 of 270 [58.1%; 95% CI, 0.52-0.64]; \( P = .00875 \)). By comparison, we observed more SNVs than expected with convergent associations with bipolar disorder (191 of 270 [70.7%; 95% CI, 0.65-0.76; \( P < 10^{-11} \)).

Genomic Structural Equation Modeling and Latent Factor PRS

Comparing our primary results with those based on latent genomic factors, we found that both schizophrenia-specific and common factor PRSs were associated with increased odds of psychosis-spectrum diagnoses (eTables 24-30 in Supplement 1). Observed protective associations of schizophrenia PRSs for sleep apnea, osteoarthritis, and hearing loss appear to be driven by schizophrenia-specific influences (eTables 24-25 in Supplement 1). The majority of associations between PRSs and broader psychiatric diagnoses and physical health problems were driven by a shared genetic liability (eTables 29-30 in Supplement 1).

Polygenic Validation of the Psychosis-Affective Spectrum

We further explored the transdiagnostic spectrum concept via hierarchical assignments of participants to schizophrenia, bipolar disorder, major depression, or related diagnoses; schizoaffective disorders, bipolar II disorder, cyclothymia, and dysthymia were considered as intermediate categories of illness and were included in analyses given adequate sample sizes (eTables 31-32 in Supplement 1). Figure 4 displays estimated PRSs estimates across disorders, comparing individuals with these disorders to a common set of screened controls.

Discussion

Building on our previous reports that published GWAS results are robustly generalizable to the US veteran population,\textsuperscript{25} we have demonstrated that the penetrance of schizophrenia PRSs is equivalent across VA and civilian health care systems, despite marked differences in absolute prevalence.\textsuperscript{10} Leveraging the VA’s extensive EHR, we confirm and extend reported associations between neuropsychiatric PRSs and broad

Figure 4. Association of Neuropsychiatric Polygenic Risk Scores (PRSs) With Psychotic and Affective Diagnoses

A. Loadings of a common factor on schizophrenia (SCZ), bipolar disorder (BIP), and major depression (MDD) results and residual variances corresponding to disorder-specific effects. B. Odds ratios per SD unit increase in PRS for selected diagnoses compared against a common set of controls; analogous results based on latent, disorder-specific PRS appear are plotted in lighter hues. Case assignments were hierarchical and nonoverlapping. DEP indicates depression; PGC, Psychiatric Genomics Consortium.

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Research Original Investigation

We focused on populations of African and European ancestry in the current study because these broadly defined ancestries comprised the majority of the CSP #572 and MVP cohorts. Our ongoing work in this area will extend these findings to diverse Asian, Hispanic, and Latino populations.

Conclusions
Application of current neuropsychiatric PRSs to the MVP yielded results consistent with multiple, continuous liability distributions underlying schizophrenia, bipolar disorder, and major depression, underscoring the advantages of multivariate and transdiagnostic approaches for studying these complex, heterogeneous clinical presentations.

Limitations
We did not attempt to model environmental or experiential differences associated with participants' military service, which may partially explain increased rates of some illnesses. We did not specifically investigate the implications of predominantly male ascertainment in MVP. CSP #572 participants largely served in the period between the Vietnam War and Gulf War conflicts, while MVP participants' service eras were more broadly distributed.

Because available EHR data are restricted to treatment received at VA facilities, any relevant medical history outside the VHA health system, including before or during participants' military service, is limited to self-report.

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Original Investigation Research

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Author Contributions: Drs Bigdeli and Voloudakis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bigdeli and Voloudakis jointly contributed to this work. Drs Harvey and Roussos jointly supervised this work. Concept and design: Bigdeli, Voloudakis, Barr, Gorman, Genovese, Conaco, O'Leary, Przygodzki, Gleason, Brophy, Huang, Aslan, Fanous, Harvey, Roussos. Acquisition, analysis, or interpretation of data: Bigdeli, Voloudakis, Barr, Gorman, Peterson, Burstein, Velcu, Li, Gupta, Mattheisen, Tomasi, Rajeevan, Sayward, Radhakrishnan, Natarajan, Malhotra, Shi, Zhao, Concasto, Pyarajan, Muralidhar, Giaoan, Aslan, Fanous, Harvey, Roussos. Drafting the manuscript: Bigdeli, Voloudakis, Barr, Gorman, Burstein, Conastto, Harvey, Roussos. Critical revision of the manuscript for important intellectual content: Bigdeli, Voloudakis, Barr, Gorman, Genovese, Peterson, Velcu, Li, Gupta, Mattheisen, Tomasi, Rajeevan, Sayward, Radhakrishnan, Natarajan, Malhotra, Shi, Zhao, Conaco, O'Leary, Przygodzki, Gleason, Pyarajan, Brophy, Huang, Muralidhar, Giaoan, Aslan, Fanous, Harvey. Statistical analysis: Bigdeli, Voloudakis, Barr, Gorman, Peterson, Burstein, Li, Rajeevan, Sayward, Shi, Zhao, Fanous, Roussos. Obtained funding: Conaco, Conasto, Przygodzki, Pyarajan, Muralidhar, Giaoan, Aslan, Harvey, Roussos. Administrative, technical, or material support: Bigdeli, Voloudakis, Peterson, Burstein, Mattheisen, Radhakrishnan, Conaco, O'Leary, Przygodzki, Gleason, Brophy, Huang, Muralidhar, Giaoan, Aslan, Harvey, Roussos. Supervision: Bigdeli, Voloudakis, Genovese, Natarajan, Conaco, O'Leary, Pyarajan, Huang, Muralidhar, Giaoan, Aslan, Fanous, Harvey, Roussos. Conflict of Interest Disclosures: Dr Malhotra reported receiving consulting fees from Jansen Pharmaceuticals, Acadia Pharmaceuticals, Informed DNA, and Genomind outside the submitted work. Dr Harvey reported personal fees from Alkermes, Karuna Pharma, Merck Pharma, Minerva Pharma, and Sunovion Pharma outside the submitted work; and royalties from WCG Verasci outside the submitted work. No other disclosures were reported.

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REFERENCES


